



# ANNALS OF INTERNAL MEDICINE

MAURICE C. PINCOFFS

Editor

PAUL W. CLOUGH

Acting Editor

VOLUME 21

(OLD SERIES, VOLUME XXVI)

July to December, 1944





# Contents

NUMBER 1, JULY, 1944

The Great Need for Internists in the Naval Medical Program. ROSS T. MCINTIRE.....	1
Demerol: A New Synthetic Analgetic, Spasmolytic and Sedative Agent. I. Pharmacologic Studies. FREDRICK F. YONKMAN, PAUL H. NOTH and HANS H. HECHT.....	7
Demerol: A New Synthetic Analgetic, Spasmolytic and Sedative Agent. II. Clinical Observations. PAUL H. NOTH, HANS H. HECHT and FREDRICK F. YONKMAN.....	17
Serum Amylase in Mumps. I. L. APPLEBAUM.....	35
Rheumatic Fever: Diet as a Predisposing Factor. DON CARLOS PEETE.....	44
Short P-R Interval Associated with Prolongation of QRS Complex; A Clinical Study Demonstrating Interesting Variations. OSCAR A. PALATUCCI and JAMES E. KNIGHTON.....	58
I. The Treatment of Experimentally Produced Staphylococcal Tho- racic Empyema. WILLIAM E. EVANS, JR., JAMES G. MCALPINE, BENEDICT SKITARELIC and E. HOWARD TONOLLA.....	70
Spontaneous Complete Rupture of the Aorta without Dissecting Aneu- rysm with Report of a Case Showing a New Physical Sign (Peri- aortic Friction Rub). FREDERICK R. TAYLOR and ROBERT P. MOREHEAD.....	81
An Evaluation of the Dark Test. PAUL H. WOSIKA.....	101
The Effect of Certain Antacids in Man as Measured by a Simplified Method for the Continuous Recording of Gastric pH. N. E. ROS- SETT and JAMES FLEXNER.....	119
Case Reports:	
Pheochromocytoma of the Adrenal Associated with Persistent Hy- pertension. GEORGE W. THORN, JOSEPH A. HINDLE and JOHN A. SANDMEYER.....	122
A Case of Transient Successive Pulmonary Infiltration (Loeffler's Syndrome) Associated with Trichiniasis. JAMES F. SLOWEY..	130
A Case of Nitrobenzene Poisoning. ZOLTON T. WIRTSCHAFTER and RALPH WOLPAW.....	135
Longevity in Ventricular Aneurysm; Report of a Case Followed over a Ten Year Period. DENNISON YOUNG and JOHN B. SCHWEDEL.....	141
Editorial.....	150
Reviews.....	153
College News Notes.....	156

## NUMBER 2, AUGUST, 1944

Glycosuria in Meningitis. FRANK FERGUSON and DAVID BARR.....	173
The Waterhouse-Friderichsen Syndrome: Observations on Associated Adrenal Insufficiency and Report of Four Cases. STUART W. COSGRIFF.....	187
Meningococcic Meningitis—Sulfadiazine Therapy (Review of Twenty Cases). EMIL H. GRIECO and ARTHUR M. COVE.....	194
Meningococcemia without Meningitis: A Study Made at the Station Hospital, Fort George Meade, Maryland. HAROLD W. POTTER, ROGER D. REID and LEWIS H. BRONSTEIN.....	200
Medical Problems in the Middle East. CRAWFORD F. SAMS.....	215
Heterophile Antibody Reaction in Infectious Mononucleosis. ROBERT E. KAUFMAN.....	230
"Atypical" Coronary Disease in Young People. JOSEPH WEINSTEIN..	252
Syphilis and Diabetes Mellitus: A Long-Term Clinical Study. FRANK S. PERKIN.....	272
Cirrhosis of the Liver; An Analysis of 71 Cases. I. DONALD FAGIN and FRANK M. THOMPSON.....	285
Some Notes on the Transmission of Heart Murmurs. SAMUEL A. LEVINE and WILLIAM B. LIKOFF.....	298
Case Reports:	
Patent Ductus Arteriosus with Pulmonary Vascular Sclerosis and Cyanosis. CARLETON B. CHAPMAN and STANLEY L. ROBBINS	312
Fatal Agranulocytosis Following the Intra-Peritoneal Implantation of Sulfanilamide Crystals. WILLIAM R. ARROWSMITH, BARBARA BINKLEY and CARL V. MOORE.....	323
Hyperparathyroidism, with Failure to Recalcify after Removal of Parathyroid Adenoma. CHARLES P. VOLTZ and KATHARINE SMULL.....	329
Uncontrollable Hemorrhage after Dicoumarol Therapy with Autopsy Findings. EDMUND L. SHLEVIN and MAX LEDERER....	332
Editorial.....	343
Reviews.....	347
College News Notes.....	350

## NUMBER 3, SEPTEMBER, 1944

Traumatic Neuroses in Court. HUBERT WINSTON SMITH and HARRY C. SOLOMON.....	367
The Dietary Factor in the Etiology of Pernicious Anemia. JOHN MARTIN ASKEY.....	402
Psychotherapy. S. KATZENELBOGEN.....	412

Impending Myocardial Infarction. LEO WAITZKIN.....	421
A Clinico-pathologic Study of 100 Cases of Acute and Chronic Gall- Bladder Disease. WILLIAM JOHNSON, B. E. MALSTROM and BRUNO W. VOLK.....	431
Subclinical Vitamin Deficiency. V. The Assay of Subclinical Thiamin Deficiency. MILDRED CARLEEN HULSE, NORMAN WEISSMAN, EL- MER STOTZ, MARSHALL CLINTON and JOSEPH W. FERREBEE.....	440
Hemoptysis in Tuberculosis, with a Differential Discussion of Other Causes. LEWIS J. MOORMAN.....	447
Direct Measurements of the Effects of Bromides, Sodium Amytal and of Caffeine in Man. EDMUND JACOBSON.....	455
Some Clinical Characteristics of Mumps, and the Effect of Belladonna in Treatment; A Study Made at the Station Hospital, Fort George G. Meade, Maryland. HAROLD W. POTTER and LEWIS H. BRONSTEIN	469
Case Reports:	
Sarcoidosis with Uveoparotid Fever. WILLIAM M. M. KIRBY and CHARLES D. ARMSTRONG.....	475
Rupture of Abdominal Aorta into Duodenum (Through a Sinus Tract Created by a Tuberculous Mesenteric Lymphadenitis). HERMAN L. FROSCH and WILLIAM HOROWITZ.....	481
Large Interauricular Septal Defect Associated with Tuberculosis and Amyloidosis. BENJAMIN J. ELWOOD and ISADORE E. GERBER	485
Editorial.....	494
Reviews.....	497
College News Notes.....	499
Postgraduate Courses by the American College of Physicians, Autumn, 1944.....	522

## NUMBER 4, OCTOBER, 1944

Rôles of Medicine and Surgery in the Management of Bronchiectasis. JOHN ALEXANDER.....	565
Sternal Puncture as a Practical Diagnostic Procedure. SIMON PROPP and JOSEPH L. SCHWIND.....	580
Kala Azar: A Review of Its Incidence and Epidemiology in China and Clinical Observations on 585 Cases. FREDERICK G. SCOVEL.....	607
Periarthritis Nodosa: Our Present Knowledge of the Disease. MARSH MCCALL and JOHN WINTHROP PENNOCK.....	628
Periarthritis Nodosa, with Report of Three Cases Diagnosed During Life. SAUL SOLOMON, MILOSH KASICH and NATHAN KIVEN.....	638

An Electrocardiographic Study of Cardiac Aging Based on Records at Rest and After Exercise. MILTON MAZER and JOHN A. REISINGER	645
Leukocytosis and the Sympathetico-Adrenal System. F. B. CLARE, C. H. CRESS and E. GELLHORN.....	653
Extrarenal Uremia: Report of Two Cases Due to Pyloric Obstruction. EDWARD J. O'DONOVAN and FRANCIS D. MURPHY.....	662
Case Reports:	
Chylothorax: Brief Review of Literature; Report of Three Non-Traumatic Cases. WILLIAM E. JAHSMAN.....	669
Chordomata: A Review of the Literature, with Report of a Sacrococcygeal Case. DANIEL B. FAUST, HUGH R. GILMORE, JR. and CHARLES S. MUDGETT.....	678
The Diagnosis and Treatment of Congenital Hemolytic (Spherocytic) Jaundice; Report of a Case with Unusual Blood Findings Altered by Liver Therapy. HENRY B. SUTTON and NORMAN S. MOORE.....	698
Acute Hemolytic Anemia with Toxic Hepatitis Caused by Sulfadiazine. DOUGLAS DONALD and RICHARD E. WUNSCH.....	709
Spontaneous Pneumothorax and Bronchial Asthma. HUGO T. ENGELHARDT and VINCENT J. DERBES.....	711
Editorial.....	718
Reviews.....	722
College News Notes.....	729

## NUMBER 5, NOVEMBER, 1944

Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension. I. Renal Aspects. A. C. CORCORAN and IRVINE H. PAGE.....	747
Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension. II. Cardiac Aspects. R. D. TAYLOR, K. G. KOHLSTAEDT, A. B. RICHTER and IRVINE H. PAGE.....	765
Rupture of the Heart in Myocardial Infarction. Experience in a Large General Hospital. SIDNEY FRIEDMAN and PAUL D. WHITE.....	778
Rupture of the Heart in Patients in Mental Institutions. WALTER W. JETTER and PAUL D. WHITE.....	783
Kerosene Intoxication. W. B. DEICHMANN, K. V. KITZMILLER, S. WITHERUP and RALPH JOHANSMANN.....	803
Syndrome of Auriculoventricular Accessory Pathway. GEORGE KAPLAN and THEODORE D. COHN.....	824

The Syndrome of Paroxysmal Tachycardia with Short P-R Interval and Prolonged QRS Complex, with Report of Two Cases. JULIUS R. PEARSON and ALBERT W. WALLACE.....	830
Choline as an Adjuvant to the Dietary Therapy of Cirrhosis of the Liver. A. H. RUSSAKOFF and HAROLD BLUMBERG.....	848
Primary and Secondary Myelofibrosis (A Clinical and Pathological Study of Thirteen Cases of Fibrosis of the Bone Marrow). LOWELL A. ERF and PETER A. HERBUT.....	863
Case Reports:	
Simmonds' Disease with Therapeutic Response to Hormone Therapy for Four Years: Report of a Case with Necropsy Findings. WARD DARLEY, ROBERT W. GORDON and KARL T. NEUBUERGER.....	890
Electrocardiographic Record of a Dying Heart. SOLOMON KRELL.....	903
Wolff-Parkinson-White Syndrome Simulating Myocardial Infarction. HERBERT EICHERT.....	907
Editorial.....	913
Reviews.....	917
College News Notes.....	920

## NUMBER 6, DECEMBER, 1944

A High Fluid Intake in the Management of Edema, Especially Cardiac Edema. II. Clinical Observations and Data. F. R. SCHEMM.....	937
The Leukocyte Count in Primary Atypical Pneumonia of Undetermined Etiology. OVID O. MEYER and ETHEL W. THEWLIS.....	977
The Use of Benzedrine Sulfate in Obesity. FREDERICK K. ALBRECHT..	983
Migraine Headache: Some Clinical Observations on the Vascular Mechanism and Its Control. MILES ATKINSON.....	990
Spontaneous Mediastinal Emphysema. HENRY MILLER.....	998
Spontaneous Pneumothorax: A Report of Three Unusual Cases. ALFRED GOLDMAN and HAROLD ROTH.....	1011
Lupus Erythematosus (Erythematoses) and Ovarian Function: Observations on a Possible Relationship, with Report of Six Cases. EDWARD ROSE and DONALD M. PILLSBURY.....	1022
Case Reports:	
Ligation of Patent Ductus Arteriosus in the Presence of an Apparent Bacterial Endocarditis: Report of a Case Apparently Cured. RALPH B. BETTMAN and WILLIAM TANNENBAUM.....	1035
Trichinosis: A Sporadic Outbreak with Report of a Case. JAMES S. SWEENEY, FRANK B. QUEEN and THOMAS F. BARRETT.....	1037

Dermatitis Due to Barbiturates: Report of a Case with Associated Anemia. J. K. POTTER and R. J. WHITACRE.....	1041
Sickle Cell Anemia Simulating Coronary Occlusion. S. L. ZIMMERMAN and ROY BARNETT.....	1045
Editorial.....	1050
Reviews.....	1053
College News Notes.....	1056
Index.....	1081

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 21

JULY, 1944

NUMBER 1

---

## THE GREAT NEED FOR INTERNISTS IN THE NAVAL MEDICAL PROGRAM \*

By ROSS T. MCINTIRE, Vice Admiral, Medical Corps, U.S.N., F.A.C.P.,  
The Surgeon General of the Navy

Our outstanding President, Dr. Paullin, has given so much to the war effort that I want to take this opportunity to express to him the thanks and appreciation of the Navy for the splendid work he has done. In addition to his being President of our College, and President of the American Medical Association, he has assumed an added responsibility as Honorary Consultant to the Secretary of the Navy and the Surgeon General of the Navy. I can assure you that as he relinquishes the details of the two positions which he now holds in civil-medicine, we in the Naval Service will call upon him for all the time he can reasonably give, and you, knowing him, can imagine what that will be.

I think I should tell you at this time just what this small group of Honorary Consultants do for the Medical Department of the Navy. They have been perfectly unselfish in the time they have given. I have sent them over all parts of the Continental United States, and even overseas, where they have inspected our various medical facilities, bringing back to me complete reports on how our activities are functioning. We have our over-all medical inspectors, men of ability and long experience in naval affairs, but these men from civil life bring a new viewpoint which has proved tremendously valuable. We expect to continue to use them throughout this war and I can assure you that they are helping immeasurably in the achievement of greater efficiency.

It must be extremely satisfying to the members of the College to see the great strides that have been made in scientific medicine in these past two years. Extremely satisfying, because you have all had a part in it. As far as medicine is concerned, this war effort is being prosecuted not only by the men in the Service, but because of the wise use that is being made by the

---

\* Presented by Rear Admiral Luther Sheldon, Jr., Medical Corps, U.S.N., at the Scientific War Session, American College of Physicians, Palmer House, Chicago, Illinois, April 1, 1944.



Army and the Navy of key people in civil life, it becomes a joint effort. Consider, too, that the Medical Departments of the Army and the Navy are made up with a tremendous majority of Reserve Officers. In fact, out of 11,000 officers in the Navy, 9500 of them are Reserve Officers.

There is one disturbing factor, however, that has come to the fore, and only recently so—it is the fact that we do not have a sufficient number of internists in the Service. A few years ago the reverse was true. I will use an illustration to show you why that is true. In our early work in the South Pacific, sanitary and tropical disease control was very difficult of accomplishment. This was due, in the main, to the lack of competent, trained men to put our plans into operation. When the Seabee battalions were formed, it was arranged for a certain number of men in each battalion to be especially trained in sanitary engineering and malaria control. Thus, we made rapid strides in cutting down the incidence of certain tropical diseases. As the tempo of the war picked up, however, the spectacular side came quickly to the fore, such as construction of airports, aiding in the landing of troops on beachheads and, in fact, taking a rather active part in the combat necessary to secure a foothold on the beaches. What happened? When we wished to set up a Mobile Hospital, or put in some drainage ditches to make a camp-site livable, these men were not to be found, because they preferred the spectacular work with the combat troops. So it is with the man who does internal medicine. He is not in the spectacular side of the field. In other words, the young man in medicine wishes to be a surgeon. He wants to do traumatic surgery—orthopedic surgery—plastic surgery—for this type of work takes him into the foreground of war activity and the man of internal medicine does his hard plugging unseen.

As I have said many times before, it will never do for us to over-specialize in the Naval Service. Surely, in time of war, it is necessary to have a rotating service so that the internist can have his chance at first aid stations and at advance base hospitals. Although the surgeon can not go into a ward and handle the cardiacs that come through, or the chronic nephritics and other difficult cases, still this man must be taught to handle acute medicine. He must know what to do about the acute respiratory diseases and he must also know what to do when he has cases of exacerbation.

We have been extremely fortunate in the Navy to be able to use our specialists in the jobs they are best equipped to handle. By actual count, we find that we have employed 72 per cent of our medical officers in the specialties in which they are trained.

A short time ago I had an opportunity to spend a great deal of time on one of our very large ships. In fact, it is one of the most modern we have. During those few weeks I was able to spend much time with our medical personnel and here I had the extreme pleasure of seeing well-trained surgeons and well-trained internists working together as a splendid team. I saw a highly trained cardiologist do a very difficult gangrenous appendix. I saw an excellent eye, ear, nose and throat man make a diagnosis on a complicated

chest condition. Here, we have men who were on their toes vying with one another to see what could be done to improve the medical service of that ship.

We have a great responsibility today to make a determination on what should be done about specialization of medicine in this country and how we should best go about doing it. I think we should give serious thought to what has happened in the past and find ways and means to prevent it from happening again, should we be forced into another war in the next twenty years.

Medical education is in a peculiarly critical period. We have a wonderful opportunity to lay down a basis for sound teaching in the pre-medical field, and in medical education itself, that should endure over a long period of time. I believe it is up to this organization to step in and take a very definite, leading part in this determination. The pre-medical field requires fully as much attention, if not more than the medical courses.

One thing I should like to call to your attention is that in our opinion visual instruction has come to stay, and in medicine it will take its place in a most decided fashion. How, then, can we best be prepared to institute this even in the days of war? There is a considerable amount of work being done, but it is rather sporadic. I can tell you that the Navy is actively at work in this field. We have teams of highly trained technicians, headed by doctors, that are in the combat zones doing a great deal of photographic work which will be prepared for teaching purposes. We are establishing photographic units in all our large hospitals, which will record for all time the technic of our various departments. Now, again, the surgical sections have a great advantage, for here the anatomical side comes in and the spectacular is there. So, I must turn to you for assistance as to methods of working out successful teaching films in internal medicine. These must be made attractive for the medical student will not tolerate dullness. We have some ideas and we have been following them. In the tropical diseases we have no such problem and we are coming up with some exceedingly interesting work. We expect to make all of this material available to teaching institutions in civil life. Very naturally, we expect to use them in our schools. I am asking you today to give thought to this in your deliberations, going well beyond what you have done in the past.

Turning now to the medical problems that we are facing, our first and foremost continues to be malaria. In this past year we had many thousands of original admissions in this disease. I do not have to tell you what that means to combat troops. We are making rapid strides in malaria control, but that is not the answer. Immunity in malaria is the thing for which we are striving.

Filariasis is a problem that will dog us for months and months to come, while we are struggling for the solution. We do have the answer to other tropical diseases and they are being handled successfully. Much is being done to develop therapy that will shorten the time on the sick list for many of the dysenteries. We expect to see results even in filariasis. Our great

trouble here is the handling of these men, for you all know that in the early stages of this disease symptoms come—then there is a period of remission during which time the patient feels quite well—following that fresh exacerbations occur from time to time and the patient who has seen the horrible end results of this disease among the Polynesians pictures himself in their plight. Thus we have a psychological problem with which to deal that can easily become psychoneurotic. Therefore, there is great need for speed in finding ways and means to handle this condition, for we have many thousands of cases.

We will continue to go on doing experimental research in all the tropical diseases with the expectation that we will find the answers to the troublesome questions that have faced medical men over such a long period of time. In other words, we will try to find the conclusive answers to the preliminary studies of such men as Manson, Strong, and Stitt.

I believe that you will be interested to know just what we have done in the field in these past two years in the way of handling our patient load. Our Hospital Program, for work beyond the continental limits, was developed with the sure knowledge that practically all these hospital facilities would be placed among the various islands of the Pacific. Our hospital units were developed so that they could subsist themselves if necessary. I am glad to tell you today that we have hospital units of 100 bed capacity and of 2,000 bed capacity, all in a more or less mobile state. I say "more or less" because these tremendous institutions are mobile up to the time we set them down. Then, of course, as the months go along and they have been in active use in their theaters, it is a real problem to tear up the buildings and move them to another site. In some instances, when we need to move a large hospital facility two thousand (2,000) miles, from the back area to the forward area, we find it more economical to set up new buildings and we simply move up the equipment.

A Unit has every modern facility that a hospital in the continental limits has. It is capable of furnishing its own electrical supply for it has a modern power plant. It has a water purification system that really works. It carries a modern laundry. Its galley equipment is a thing of beauty. The laboratory facilities are complete in every detail. The roentgen-ray equipment was designed with the help of the best engineers in this country. The workshops are air conditioned, and that has proved a great blessing to the patients and to the doctors. In many of our institutions we have at least one ward that is air conditioned so that the critically ill patients may have the benefit of it. So, you can see that we are able to do any kind of work that we are called upon to perform in these mobile units.

Since December 7, 1941, we have hospitalized over 208,000 patients in these various mobile units. The results, from such adequate hospital treatment, so close to our front lines, have paid us tremendous dividends. I can not give you the exact record of each hospital, but I can tell you that some of them have astonishing ones. One, especially, established a record

over a two year period of a mortality rate of less than 1.5 per cent. This hospital handled a majority of the battle casualties which occurred on Guadalcanal.

You might say that we are carrying on too elaborate a program, but I can not agree with this for I see no reason at all why we should spend billions of dollars to kill our enemies and only a few hundred thousands to save the lives of our men. I have no feeling whatsoever about asking for a reasonable amount of money for the hospitalization of the sick and the wounded. I am telling you all this for I want you to know just how far we have progressed in providing modern hospitalization for our men close to the battle lines.

These hospitals are made doubly useful by the use of air transportation. We have reached a point where we are now insisting that mobile hospitals be located as close to flying fields as possible, so that the patients will not have to be juggled over rough roads in transit from the field to our institutions. It will be a marvelous thing when we can do away with all forms of ambulance transportation by land, for here we have one of the greatest instruments for producing—or let me say increasing—shock.

The internist who is fortunate enough to be assigned to one of these mobile hospitals will be practicing medicine at a frontier and yet he will have every modern facility that he has in his own hospital at home. He will be the master of his own division and he will have the great satisfaction of being able to practice his specialty among the battle casualties that are efficiently moved into his hospital, where his knowledge, built up on years of experience, will be invaluable to the surgeon who will be called upon to treat the injured.

Now, I want to say a word about our Hospital Ships. I speak with a certain amount of feeling about these ships for I spent over five years of my service in such duty. I can tell you that there is no more satisfying place to practice medicine, for here you find a group of men living together, isolated, entirely dependent upon themselves. These ships do a remarkable job, for they have two duties to perform—they serve as a means of evacuation for the wounded and they receive and care for the casualties as they occur in the Fleet.

Here, again, we provide the most modern equipment that is known. The internist who is head of his department on one of these ships will have every known means, in a mechanical way, to improve the handling of his patients. These ships carry everything in the way of laboratory equipment. Their roentgen-ray plants are modern and they carry all of the luxury equipment with which we feel we must practice medicine today. In other words, a basal metabolism is a routine practice; the electrocardiograph has long been standard equipment—and I could go on and on.

On a Hospital Ship we practice medicine in a different fashion, for here every medical officer has an opportunity to see every critical case that comes on board. The internist becomes a fair surgeon; the surgeon learns again

something about internal medicine; and the ophthalmologist finds that there is such a thing as the practice of medicine. I can say this for I know something about that specialty. My only complaint is that our doctors in the isolated specialties, in civil life, are too busy to be able to see enough of medicine.

Perhaps, I may sound as though I am bragging about the practice of medicine in the Navy. I am not. I have simply been stating facts. I will be very glad to brag about the splendid way in which the Reserve Officers have stepped into the organizations which I have just described. As I have said earlier in my remarks, you should feel as proud as I do of your fellows who are serving with the Armed Services.

I suppose this war will bring about many new things that will be of great constructive value to medicine. I am perfectly sure, however, that the greatest thing it will bring about is the understanding that doctors will have among themselves. This war is not lasting just a few months; it is lasting over a period of years. I am of the firm conviction that we have several more years to go. Because of that fact men will learn the great value of close association in medical practice and I am hoping that out of this war will come sound opinions as to what we can do in civil medicine to have closer association among our doctors.

In closing I want to say a word about the necessity for postwar planning. Your outgoing President is performing a leading rôle in this. He realizes, as I do, that medicine must make a real contribution in these plans. We have seen many danger signs from people who are not qualified, but who are proposing plans for medicine. I am firmly convinced that plans must be made. We must find ways and means to provide medical and hospital care for the thousands of men and their families who will be attempting to find a place to live following this war. The shifting population that must settle down again will add to our difficulties. The doctor's fee is not a problem, for I feel very definitely that the good doctor still practices medicine and too often forgets his fee. We must find ways and means also to reduce the collateral costs of medical and hospital care. I hope the American College of Physicians will take a leading part in this and that it will clearly and unselfishly review the events which have led up to this necessity and offer sound and concrete suggestions.

# DEMEROL: A NEW SYNTHETIC ANALGETIC, SPASMOLYTIC AND SEDATIVE AGENT. I. PHARMACOLOGIC STUDIES \*

By FREDRICK F. YONKMAN, M.D., PAUL H. NOTH, M.D., M.S., and  
HANS H. HECHT, M.D., *Detroit, Michigan*

THE disadvantages attending therapeutic use of morphine and other analgetics have impelled investigators in numerous fields of medical endeavor to seek an adequate substitute for the relief of pain. Codeine, dilaudid, snake venom and other agents recently introduced do not subscribe in every respect to the specification of 'adequate substitute' because of various side-effects or other disadvantages associated with each. However, a synthetic substance which in some respects equals or surpasses morphine is available in demerol. It appears in the literature under various names such as Dolantin, Dolantol, D-140, S-140, and more recently as Demerol, which is the most generally accepted term in this country.

We have studied the drug pharmacologically and clinically. The results of a clinical study of demerol as a morphine substitute both in acute and chronic conditions will be presented in a subsequent article. In this present report we wish to review briefly its chemical features and pharmacologic properties and to present the results of our animal and human studies of its effects on smooth muscle of the uterus and intestine. For a more detailed consideration of its general pharmacologic properties the reader is referred to the work of Schaumann <sup>2</sup> and Gruber, Hart and Gruber.<sup>7</sup>

## CHEMISTRY

Demerol was synthesized in 1939 by Eisleb and Schaumann <sup>1</sup> as the ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid. This is a white, insoluble crystalline substance which becomes soluble in water as the hydrochloride salt. In this paper, the term demerol implies the hydrochloride form. It is slightly bitter and is non-irritant to the gastrointestinal mucosa. At one time the carboxylic acid modification was of interest because of its peripheral or local anesthetizing potentialities, but in the ethyl ester form it attracted greater interest because of its analgetic and spasmolytic actions.

A study of the chemical formula proposed by Schaumann <sup>2</sup> indicates the relation of demerol to atropine and also to morphine. The latter has been commonly accepted as a derivative of phenanthrene, but Gulland and Robin-

\* Received for publication July 10, 1943.

From the departments of Pharmacology and Therapeutics and of Medicine of Wayne University and from the department of Medicine of Receiving Hospital and the Medical Division of the William J. Seymour Hospital. This interdepartmental study of demerol hydrochloride received the support of Dr. J. Mark Hiebert of the Alba Pharmaceutical Division of the Winthrop Chemical Company, Inc. The project was aided by the A. Mendelson Memorial Fund of Detroit.

# ATROPIN, DEMEROL (Dolantin), and MORPHINE (Schaumann.)

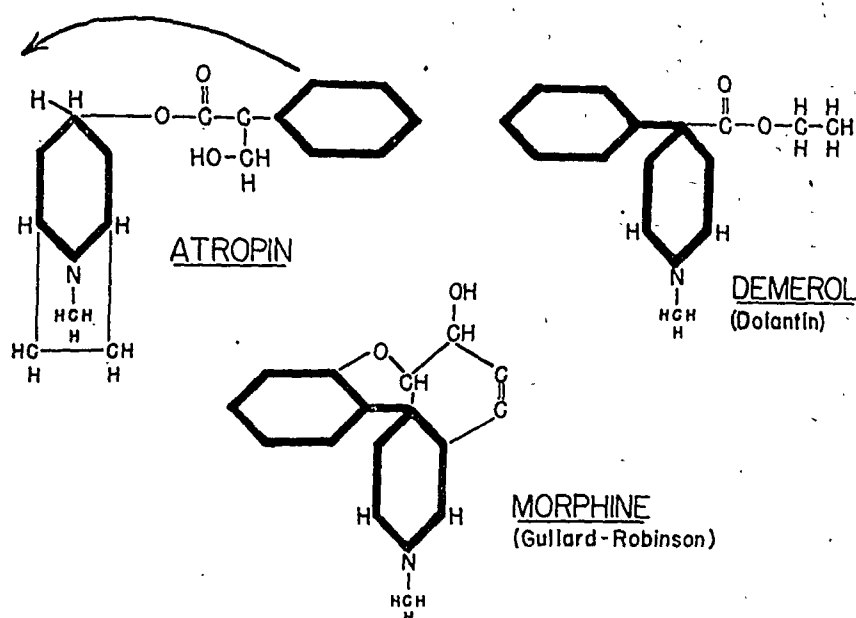


FIG. 1.

son<sup>3</sup> have proposed the piperidine formulation pictured in figure 1. If this be the true formula for morphine, not only is the chemical relation of demerol to morphine and atropine apparent but the atropine and morphine-like pharmacologic actions of demerol become easier to understand.

## PHARMACOLOGY

*General Actions.* Demerol has been studied pharmacologically by several investigators<sup>1, 2, 4, 5, 6, 7, 8, 9, 10</sup> both in this country and in Europe. It resembles atropine in its anticholinergic action in the production of mydriasis, suppression of saliva, insulation of the heart, bronchi and intestine against vagal stimulation. It resembles papaverine in its spasmolytic action since it also directly relaxes the bronchi, intestine, uterus and blood vessels. Demerol resembles morphine in its capacities to produce analgesia, sedation, euphoria and, at times, side-effects somewhat similar to those produced by morphine.

*Toxicity.* Acute toxicity studies have been reported<sup>7</sup> in which the M.L.D. 50 of demerol was 221 mg. per kg. orally and 147 mg. per kg. intraperitoneally in white mice, but 93 mg. per kg. intraperitoneally in white rats. In rabbits, the intravenous M.L.D. 50 ranged between 20 and 32 mg. per kg. depending upon weight of the animals employed.

Chronic toxicity studies<sup>7</sup> showed that white mice tolerated 90 mg. per kg. daily by mouth for 25 days without manifesting any ill effects. Gruber also fed four dogs 50 mg. per kg. of demerol by mouth daily, six days a week

for five weeks. Salivation, some nausea, and rare vomiting, with definite evidence of distaste for the drug resulted after the first week. After five weeks Gruber increased the daily dose to 100 mg. per kg. Two dogs survived a total of 12 doses at the higher level and "at no time during the entire seven weeks was the blood picture of any animal significantly different from the control." Barlow<sup>9</sup> treated eight adult dogs with a daily dose of 75 mg. per kg. and 24 monkeys with 40 mg. per kg. daily for 10 months. "Although a slight degree of anorexia and a slight falling off in weight were observed no deleterious effect was produced with respect to the hematopoietic system nor upon necropsy were any histologic changes in liver, kidneys, spleen, gastric mucosa, or bone noted."

Acute and chronic toxicity studies in man are reported in the clinical paper.<sup>11</sup>

*Uterine Responses.\** Isolated strips from guinea pigs, virgin and non-virgin, were studied in tissue baths ordinarily used for these experiments in which the muscle is bathed in Locke's solution, pH 7.5 to 7.6 at 39° C., and contracture changes are recorded on the kymograph. Figure 2 illustrates the typical results which were almost uniformly obtained in over 55 experi-

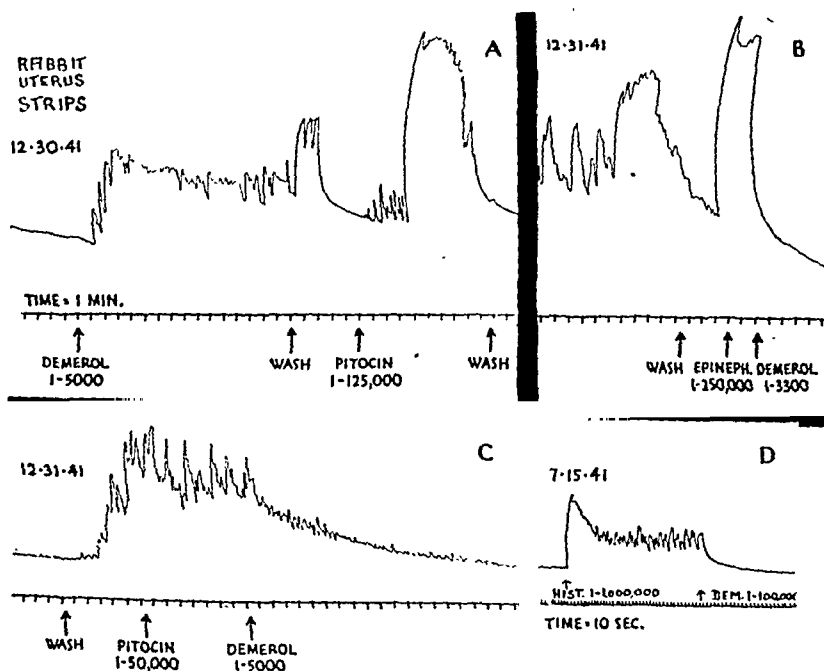


FIG. 2. Kymographic records of uterine strips of rabbits and their responses to:

- A. Demerol, 1-5000 and pitocin, 1-125,000
- B. Epinephrine, 1-250,000 and demerol, 1-3300
- C. Pitocin 1-50,000 and demerol, 1-5000
- D. Histamine, 1-1,000,000 and demerol, 1-100,000

Time = 10 minute intervals in A, B and C and 10 seconds in D.

\* We are grateful to Dr. Marshall Purdy and Dr. Garnett Ice for their coöperation in these experiments.



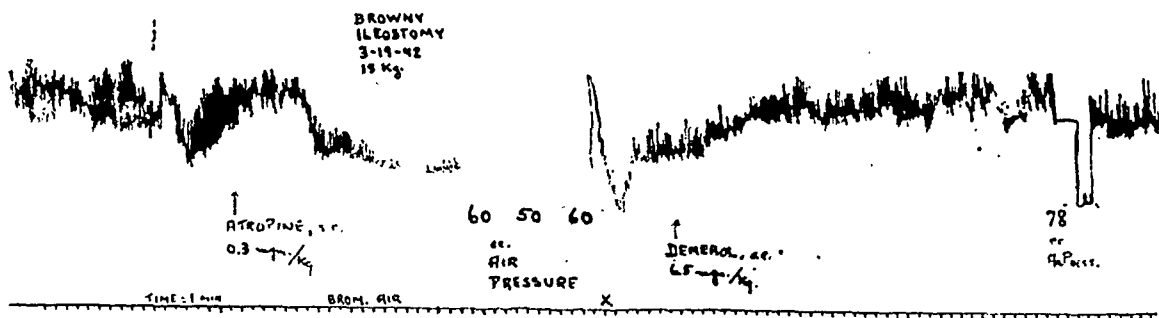


FIG. 3. Tracing of ileum of unanesthetized dog with balloon inserted through ileostomy. Atropine, 0.3 mg. per kg. subcutaneously, followed by demerol, 6.5 mg. per kg. subcutaneously. Figures 60, 50 and 60 indicate volume of air in c.c. required to elicit painful response to distension before demerol and 78 c.c. denotes average volume required to elicit similar response after demerol.

Time = 1 minute intervals.

ments. Demerol usually relaxed the segment which had previously been activated either by epinephrine, 1–1,000,000 to 1–250,000, pitocrin, 1–125,000 to 1–50,000, histamine, 1–10,000,000 to 1–1,000,000, barium chloride, 1–10,000 or physostigmine, 1–20,000. The degree of relaxation or inhibition depended upon the dose of stimulant as well as that of demerol. Demerol was an effective spasmolytic in a dose of 1–100,000 on a uterus under strong histamine stimulation as illustrated in figure 2, D. Frequently, but by no means consistently, demerol activated the flaccid, previously untreated uterine strip (figure 2, A). Our results amply confirm previous work<sup>2, 7</sup> in that the flaccid uterus may be stimulated, whereas relaxation usually ensues in the tonic or active segment.

*Intestinal Responses.* Balloon experiments, the technic of which has been described previously,<sup>12</sup> were conducted 12 times in four trained, un-

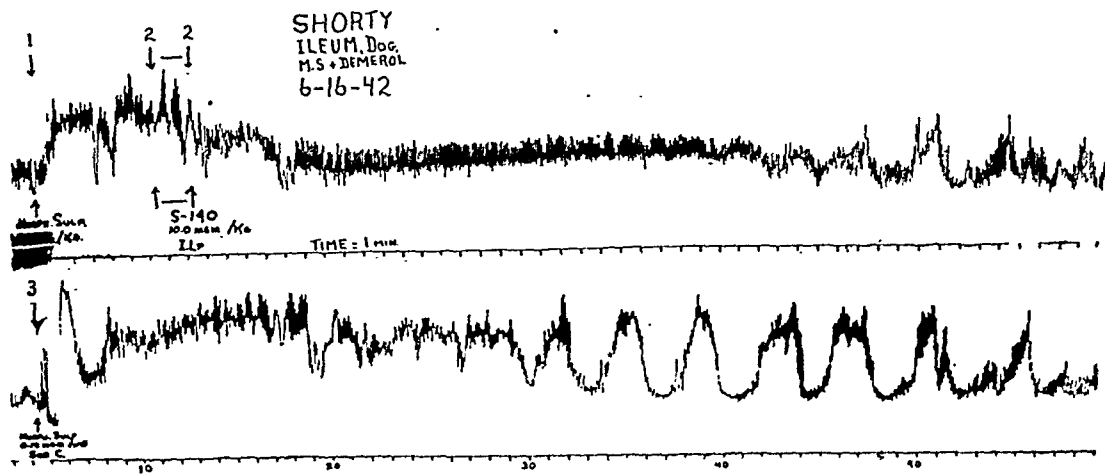


FIG. 4. Dog, unanesthetized, tracing of ileum. Drugs administered subcutaneously in following order: morphine sulphate, 0.1 mg. per kg., demerol (S-140) 10 mg. per kg., morphine sulphate, 0.1 mg. per kg.

Time = 1 minute intervals.

anesthetized dogs with ileostomies or with Thiry-Vella loops of ileum. Our experiences were similar to those of Grüber,<sup>7</sup> since the normal dog ileum was uniformly stimulated in tone, peristalsis and segmentation. These effects were evident even after atropine had rendered the intestine almost quiescent (figure 3). However, if morphine had first been administered to activate the intestine<sup>12</sup> as was the case in six experiments, even to the point of vomiting, demerol markedly depressed some phases of intestinal activity (figure 4) and especially segmentation (figure 5). These findings do not agree with those of Grüber who states<sup>7</sup> "As far as could be determined, this latter injection (Demerol) had no significant effect upon the morphine re-

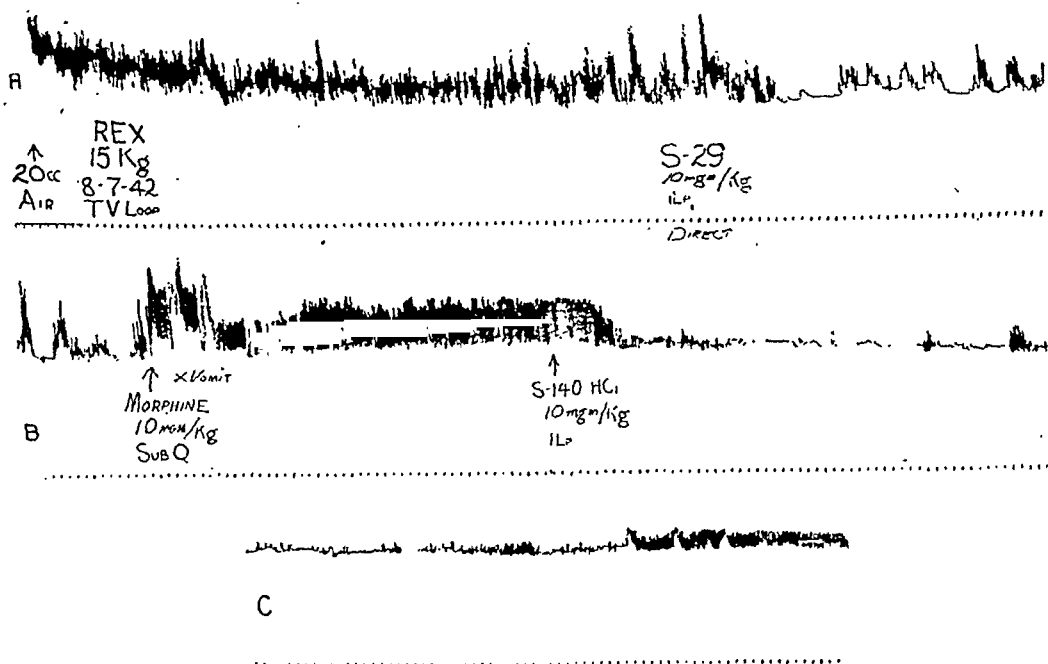


FIG. 5. Dog, unanesthetized, tracing of ileum. Drugs administered subcutaneously in following order (B): morphine sulphate, 1.0 mg. per kg., demerol (S-140), 10. mg. per kg. inserted through ileostomy. Recovery from relaxation approaches in C.

Time = 1 minute intervals.

sponse." We have not attempted to activate the intact intestine by any other agents, but it would be of value to study the tranquilizing effect of demerol after pituitrin, physostigmine or concentrated sodium chloride given intravenously.<sup>13</sup>

If the intestinal stimulating action of demerol in the dog should find its counterpart in the human intestine, the drug might be useful in the treatment of postoperative ileus and of diarrhea. Therefore, intestinal motility studies were conducted in patients\* with ileostomies, cecostomies, colostomies or with the indwelling Miller-Abbott tube at various levels of the gastroin-

\* We are grateful to Drs. R. Crowley, J. T. Downs, M. H. Blau, L. Whelan, J. Posch, B. N. Craver and R. Bauer for their cooperation in this phase of the work.

testinal tract. Intestinal contractions were registered against air distended balloons which were attached to catheters; these were in turn connected with a bromoform manometer whose float transmitted contraction waves against a smoked kymographic paper. Fifteen experiments were conducted on five patients and in only one instance was there evidence of stimulation after demerol. This occurred in one experiment on a patient who on four other occasions had no colonic stimulation after demerol. Figure 6 reveals that

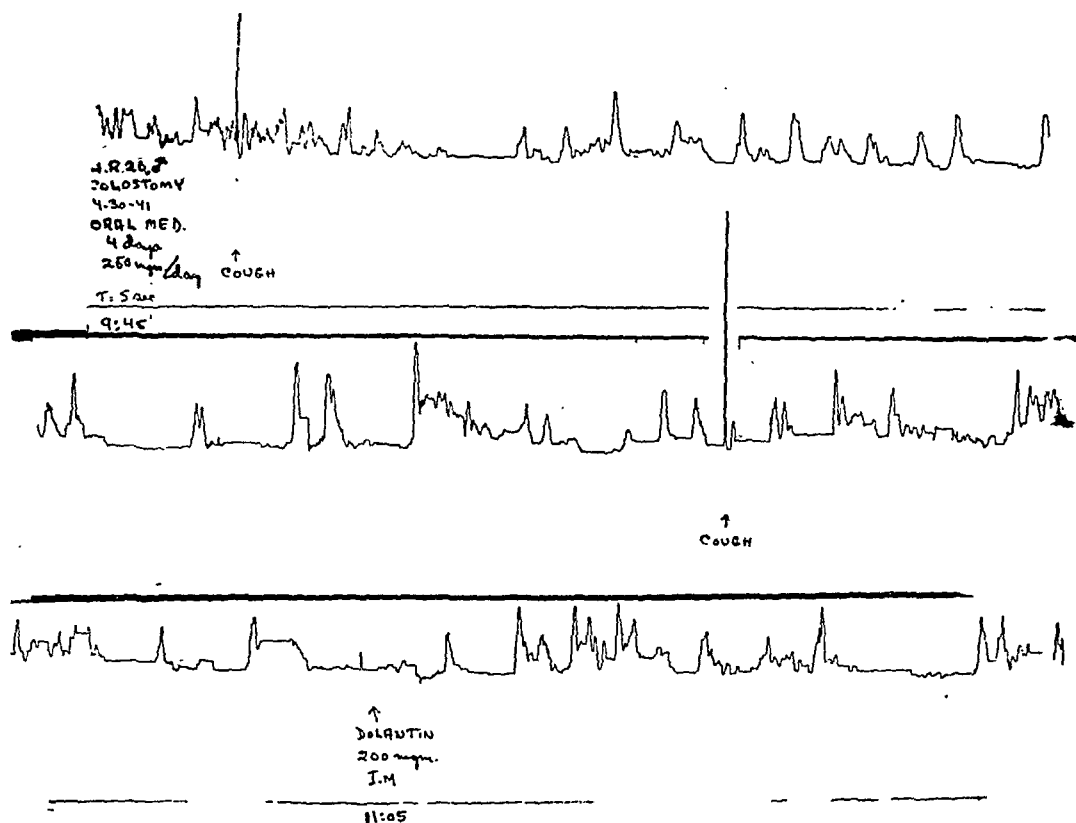


FIG. 6. Patient, H. R., age 26, colostomy. Tracing of colonic activity after patient had received 250 mg. of demerol orally for four days. No appreciable effect observed. Demerol (dolantin), 200 mg. intramuscularly likewise produced no significant change.

Time = 5' second intervals.

daily oral medication with 250 mg. per day for four days followed by 200 mg. intramuscularly failed to alter the normal motility of his colon. This patient was of special interest because in two experiments demerol failed to check tone increase by morphine and even in large doses demerol interfered in no way whatever with his ward ambulations or daily habits.

The quiescent effect of demerol on the human ileum is observed in figure 7. Normal peristaltic frequencies were aborted for almost 40 minutes, after which morphine was capable of exerting its normal tone increasing or "splinting" effect upon the ileum.<sup>12</sup> The absence of kymographic evidence of intestinal stimulation was verified by the patients' persistent negation when

questioned concerning "cramp-like pain or colic" after demerol injections. This was not true in our morphine studies.<sup>12</sup>

In none of our experiments with demerol was there evidence of a lessened intestinal tone, save one, which developed gradually over a period of approximately one and one-half hours. What relaxing effect, if any, demerol might have in the hyperactive or spastic human intestine has not been determined with nicety but preliminary studies in three instances indicate that relaxation may ensue (figure 8). Although demerol is not spasmolytic in the pyloric sphincter of dogs,<sup>7</sup> Barlow<sup>9</sup> states that "in 27 human subjects direct intubation studies with balloons in various portions of the gastrointestinal tract reveal an antispasmodic response with 50 to 100 mg. of

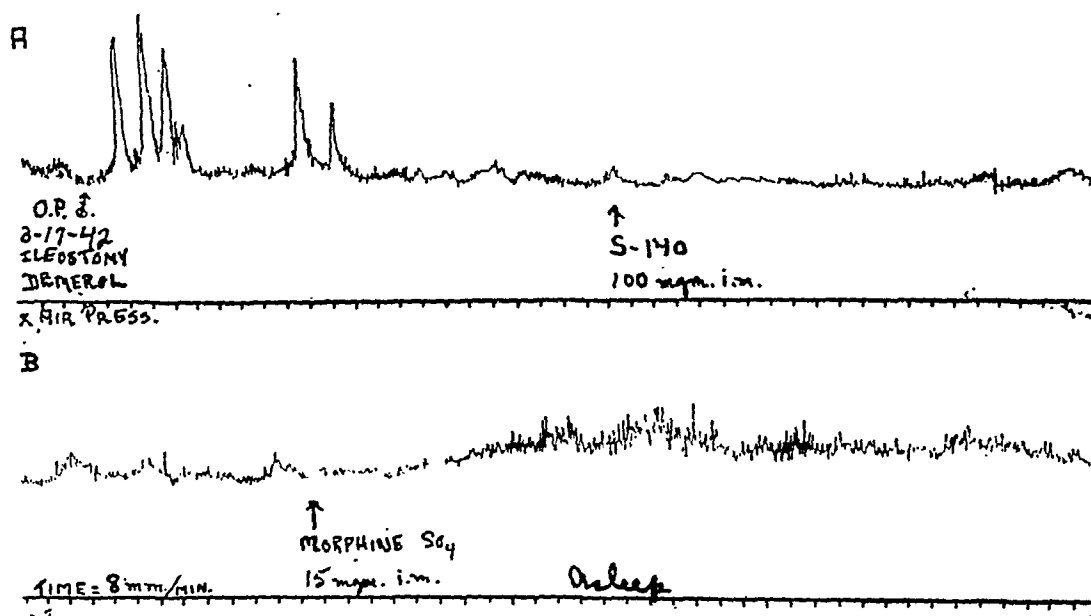


FIG. 7. Patient, O. P., age 32, ileostomy. Tracing of normal activity of ileum as relaxed by demerol (S-140), 100 mg. intramuscularly and subsequently stimulated by morphine sulphate, 15 mg. intramuscularly.

Time = 1 minute intervals.

demerol HCl intramuscularly in 23 or 84 per cent of the subjects. Complete cessation or diminution of motility occurred usually within 10 minutes and lasted from 15 to over 90 minutes." Barlow's findings have been amply confirmed by intubation studies in man by Batterman.<sup>17, 18</sup> A direct spasmolytic effect of demerol, in addition to its analgetic effect, would obviously enhance the relief obtained by altering the functional pathology responsible for the pain and discomfort. Even if relaxation did not uniformly occur, its analgetic effect might still be of sufficient degree to afford pain relief. In fact, in one experiment (figure 3) on an unanesthetized dog the analgetic effect of demerol was sufficient to allow for greater distention of the intestine before pain or discomfort was evinced. This prevailed even though demerol had increased intestinal tone.

In this experiment the dog's intestine had been quieted with atropine. The balloon was then deflated and reinflated with air from a large syringe until the dog gave visual evidence of slight discomfort. The average pain threshold of three inflations induced at three minute intervals was determined before and after demerol. The average volume of air causing discomfort in this particular experiment (figure 3) was 57 prior to demerol whereas 40 minutes after the drug the average figure was 78 c.c., even in the presence of increased tone produced by the analgetic agent. This difference of 21 c.c. of air represented a 36 per cent analgetic advantage gained by demerol. Although relatively crude in its present stage of development, refinements of this pressure balloon method may well give one a better appraisal of analgetic effects than the commonly used Hardy-Wolff light-beam technic<sup>14</sup> which evaluates analgetics not on their capacity to dampen visceral pain but only a specially induced pain (heat) on specially prepared skin areas. Since smooth muscle spasm and distention are common indications for analgetic therapy, one would be inclined to

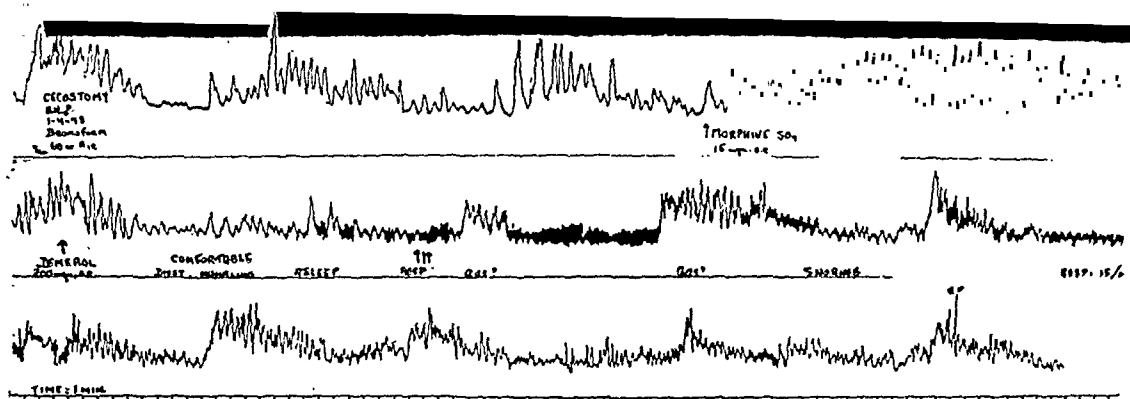


FIG. 8. Patient, A. N., age 42, cecostomy. Tracing of normal colonic activity as affected by stimulating action of morphine sulphate, 15 mg. subcutaneously and of subsequent partial inhibition by demerol, 200 mg. subcutaneously.

Time = 1 minute intervals.

believe that analgetic potency might best be evaluated from results obtained in artificially produced visceral pain as was done in these experiments. The results gained from several experiments of this type indicate a 20 to 36 analgetic potency for demerol.

The results of these studies warrant the clinical use of demerol, as is the case with morphine, in intestinal,<sup>12</sup> biliary,<sup>15</sup> and ureteral<sup>16</sup> colic, regardless of the action of the drug on smooth muscle.

#### COMMENT AND SUMMARY

Demerol hydrochloride is a safe drug. This is evident when one appreciates the high dosages administered to animals and man in toxicity studies and clinical assay.

Demerol is readily absorbed after oral, subcutaneous or intramuscular administration, producing analgesia and sedation. It exerts a weak atropine-like action as well as a moderately strong papaverine-like effect upon any

viscus containing smooth muscle. These actions are more intense when spasm or some form of stimulation prevails. However, should the functional pathology of a spastic viscus not be arrested, the failure of spasmolytic action may still be nullified or overridden by the marked analgetic action elicited by demerol.

The intestinal stimulating action of the drug uniformly produced in dogs does not prevail in man. The lack of stimulation of the intestine under demerol, particularly as regards tone increase, precludes its use as a bowel splint postoperatively. However, in the great majority of patients requiring analgetic drugs, splinting of the bowel is not a consideration and the absence of this action is an advantage since the usual constipating effect of morphine would be avoided.

The chemical configuration of demerol tends to render understandable some of its important actions in relation to atropine and morphine, its chemical relatives. It is another illustration of the fundamental principle that chemical structure or relationship frequently forecasts pharmacologic events to come. It is the principle which makes pharmacology interesting, even fascinating, and therapy rational.

#### BIBLIOGRAPHY

1. EISLEB, O., and SCHAUMANN, O.: Dolantin, ein neuartiges Spasmolytikum und Analgetikum (chemisches und pharmakologisches), *Deutsch. med. Wchnschr.*, 1939, lxxv, 967.
2. SCHAUMANN, O.: Über eine neue Klasse von Verbindungen mit spasmolytischer und zentral analgetischer Wirksamkeit unter besonderer Berücksichtigung des 1-Methyl-4-phenyl-piperidin-4-carbonsäure-äthylesters (Dolantin), *Arch. f. exper. Path. u. Pharmacol.*, 1940, cxvii, 2. Heft, 109.
3. GULLAND, J. M., ROBINSON, R., quoted by GOODMAN, L., and GILMAN, A.: The pharmacological basis of therapeutics, 1941, p. 187.
4. DUGUID, A. M. E., and HEATHCOTE, R. St. A.: Pharmacological action of ethyl methyl-phenylpiperidinecarboxylate, *Quart. Jr. Pharmacol.*, 1940, xiii, 318.
5. KIESSIG, H. J., and ORZECOWSKY, G.: Ueber die analgetische Wirkung des 'Dolantins,' *Schmerz Narkose u. Anesthesia*, 1940, xiii, 49.
6. IZAR, G., and LENZI, S.: Studi sulla Dolantin, *Rassegna internaz. di clin. e. terap.*, 1941, xxii, 215.
7. GRUBER, C. M., HART, E. R., and GRUBER, C. M., JR.: Pharmacology and toxicology of ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid (demerol), *Jr. Pharmacol. and Exper. Therap.*, 1941, lxxiii, 319.
8. YONKMAN, F. F., NOTH, P. H., and HECHT, H.: Some pharmacologic features of demerol, *Proc. Cent. Soc. Clin. Res.*, 1942, xv, 89.
9. BARLOW, O. W.: Studies on demerol (personal communication), 1942.
10. CLIMENKO, D. R.: Demerol: A pharmacologically active substance with atropine-like and morphine-like properties, *Feder. Proc.*, 1942, i, 15.
11. NOTH, P. H., HECHT, H. H., and YONKMAN, F. F.: Demerol: a new synthetic analgetic, spasmolytic and sedative agent. II. Clinical studies, *ANN. INT. MED.*, 1944, xxi, 17-34.
12. YONKMAN, F. F., HIEBERT, J. M., and SINGH, H.: Morphine and intestinal activity, *New England Jr. Med.*, 1936, ccxiv, 507.
13. YONKMAN, F. F.: Colon activation by intravenous hypertonic sodium chloride injection in unanesthetized, trained dogs, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 1207.

14. HARDY, J. D., WOLFF, H. G., and GOODELL, H.: Studies on pain. New method for measuring pain threshold: observations on spatial summation of pain, *Jr. Clin. Invest.*, 1940, xix, 649.
15. MCGOWAN, J. M., BUTSCH, W. L., and WALTERS, W.: Pressure in the common bile duct of man, *Jr. Am. Med. Assoc.*, 1936, cvi, 2227.
16. OCKERBLAD, N. F., CARLSON, H. E., and SIMON, J. F.: Effect of morphine upon human ureter, *Jr. Urol.*, 1935, xxxiii, 356.
17. BATTERMAN, R. C.: The clinical effectiveness and safety of a new synthetic analgesic drug, Demerol, *Arch. Int. Med.*, 1943, lxxi, 345.
18. BATTERMAN, R. C.: Demerol—A new synthetic analgesic, *Jr. Am. Med. Assoc.*, 1943, cxxii, 222.

# DEMEROL: A NEW SYNTHETIC ANALGETIC, SPASMOLYTIC, AND SEDATIVE AGENT. II. CLINICAL OBSERVATIONS\*

By PAUL H. NOTH, M.D., M.S. (in Medicine), HANS H. HECHT, M.D.,  
and FREDERICK F. YONKMAN, M.D., PH.D., *Detroit, Michigan*

THE chemical composition and pharmacologic properties of demerol have been described in a separate communication.<sup>1</sup> The present report deals with clinical observations of the actions of this drug. Since 1939 a great number of clinical reports on demerol (variously called Dolantin, Dolantol, Alba, D-140, S-140) have appeared in the South American and European literature including observations on more than 2,000 cases. Only a few clinical studies, however, have been published in this country,<sup>2, 3, 4, 5, 6, 7</sup> including a series of papers by Himmelsbach and Andrews on tolerance and addiction liabilities in former morphine addicts.<sup>8, 9, 10</sup> We have attempted to compare our own results with those reported in the literature.

*Material and Method of Study.* A series of 146 patients was observed. One hundred eighteen of these were suffering from various diseases in which pain was severe enough to have justified the use of one of the opiates. This includes a group of 26 patients with persistent severe pain of weeks' or months' duration. Six of these patients had been taking morphine, 13 codeine, and two dilaudid for considerable periods of time. This group of 26 patients was given demerol at regular intervals for as long as 211 consecutive days. The average duration of therapy was 51.4 days, and the average total dose 32.6 grams. Most of the remainder of the 118 patients suffered from more acute illnesses and received an average total dose of one gram during an average period of six days. Twenty-four patients without pain were studied solely for the purpose of evaluating the sedative action of demerol. A final group consisted of four patients suffering from bronchial asthma. The special clinical records included a description of the type and severity of the pain, its duration, the effect of previous medications, a description of the subjective and objective response to the individual doses of demerol, and a summary of the analgetic, sedative, and side-effects noted. Routine laboratory and roentgenographic studies were performed and in over one-half of the cases the urinalysis, hemoglobin, erythrocyte, and leukocyte estimations were repeated during or after therapy with demerol. Evidences of toxicity were looked for, particularly in the group of 26 patients

\* Received for publication July 10, 1943.

From the Departments of Medicine and of Pharmacology and Therapeutics of Wayne University College of Medicine; the Medical Departments of Detroit Receiving Hospital, and the William J. Seymour Hospital, Eloise, Michigan.

This interdepartmental study received the support of Dr. J. M. Hiebert of the Alba Pharmaceutical Division, Winthrop Chemical Company, and the A. Mendelson Memorial Fund, of Detroit.



who received the drug for a longer time. In these cases complete urinalysis and studies of the blood, including determinations of hemoglobin, the number of erythrocytes and leukocytes, and differential leukocyte counts, were repeated at weekly intervals. Electrocardiograms and bromsulphalein tests of hepatic function also were performed repeatedly in these cases.

### DOSAGE

*Summary of the Literature.* Demerol has been administered orally, intramuscularly or subcutaneously by most observers. The usual dose for adults was 100 milligrams; the dosage ranged between 50 and 200 milligrams. According to one report<sup>11</sup> heavy individuals usually required more than the average dose. Sprockhoff<sup>12</sup> states that doses for children range from 10 to 75 milligrams. Rectal suppositories have been used occasionally, especially in obstetrical cases.<sup>13</sup> When it is given intravenously, a number of unpleasant side reactions may occur and it is stated that when this route is employed the drug should be diluted and given slowly during a period of not less than two minutes.<sup>14</sup>

*Present Study.* In our cases the dose of demerol employed was, with very few exceptions, 100 milligrams, given orally or intramuscularly from one to eight times daily. In the chronic cases in which demerol was substituted for morphine or dilaudid, it was often necessary to shorten the usual four-hourly interval between doses to three hours. Because of a more prompt and, therefore, more easily evaluated response, the intramuscular route was used about twice as frequently as the oral route. Intravenous administration was avoided because of the possibility of its producing undesirable reactions and because the intramuscular injections usually produced their effects very promptly. Demerol may produce irritation when given subcutaneously and as a consequence this route also was avoided.

### ANALGETIC EFFECTS

*Summary of the Literature.* Favorable effects following the administration of demerol have been reported in a great variety of painful conditions, particularly those associated with spasm of smooth muscle. It has been reported that severe pain is satisfactorily controlled in various lesions of the gastrointestinal, biliary, and genitourinary tracts, as well as of the pancreas, pleura, and other organs.<sup>3, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23</sup> It has been considered to be effective in relieving pain associated with thrombosis or embolism of peripheral or coronary arteries.<sup>15, 16, 21</sup> It was used successfully in acute and chronic arthritides<sup>16, 22</sup> and in a variety of neurological disorders such as polyneuritis and neuralgia,<sup>16, 19, 22, 24, 25</sup> migraine,<sup>16, 24</sup> tabetic crisis and radiculitis.<sup>24, 25</sup> Its use for relief of pain occurring coincidentally in patients with multiple sclerosis led to the observation that it seemed to benefit the weakness and other symptoms of this disease.<sup>34</sup> It has been used extensively to combat pre- and postoperative pain and in other primarily surgical con-

ditions usually requiring morphine or its derivatives.<sup>4, 5, 26, 27, 28</sup> In obstetrics it has been used alone or in conjunction with scopolamine and barbiturates to control pain during labor and to aid in producing amnesia.<sup>6, 7, 13, 31</sup> It has been of value in gynecological conditions and procedures<sup>11, 17, 29, 30</sup> and in a variety of diseases of children.<sup>12</sup> Severe hiccups,<sup>32</sup> discomfort, and pain occurring during or after certain diagnostic procedures such as cystoscopy, retrograde pyelography, gastroscopy, bronchoscopy and pneumoencephalography have been claimed to be adequately controlled by demerol.<sup>18, 22, 33</sup>

### PRESENT STUDY

Table 1 summarizes the analgetic effect of demerol upon 118 patients with various diseases giving rise to the types of pain listed. Five patients

TABLE I  
Analgetic Effect of Demerol

Types of Pain	Results			
	No. of Cases	Complete Relief	Partial Relief	No Relief
Arthritic.....	9	6	2	1
Gastrointestinal.....	22	15	6	1
Biliary tract.....	5	3	1	1
Renal.....	6	6		
Nerve and thalamic pain.....	18	11	6	1
Osseous pain.....	8	3	2	3
Headache.....	18	13	2	3
Pleural.....	12	8	2	2
Cardiac.....	10	5	4	1
Miscellaneous.....	15	9	4	2
Total.....	123*	79 (64.2%)	29 (23.6%)	15 (12.2%)

\* Five patients had 2 types of pain.

had two distinct types of pain and consequently the number of instances exceeds the number of cases by five. Complete relief occurred in 79, or 64.2 per cent. Partial relief, which occurred in 29, or 23.6 per cent, usually consisted of moderate relief, sufficient to be considered as a satisfactory clinical response. No relief was obtained by 15, or 12.2 per cent. The groups with partial or no relief included four patients who had been addicted to morphine or dilaudid, and who resisted the attempted substitution of demerol for these drugs. Whenever codeine had been administered, demerol could be substituted without any trouble and was always claimed to be superior in its analgetic effect. The time of the onset of relief was from five to 20 minutes following intramuscular injection, and from 20 to 30 minutes following oral administration. The duration of the relief varied between one and six hours, but was usually three or four hours. Relief was more often complete, as well as more rapid, following intramuscular use.

The results in each type of pain are considered separately in the following paragraphs.

*Arthritic Pain.* Five of the nine patients in this group were suffering from acute gonorrheal arthritis and one each from streptococcal arthritis, tuberculous arthritis, traumatic arthritis, and polyarthritis associated with Hodgkin's disease. Relief of pain by 100 milligrams of demerol was complete in six, partial in two, and absent in one. The intramuscular route gave results which were superior to those obtained by oral administration in three of five patients in whom the comparison was made, and equal results in the two remaining patients. In five patients the analgetic effect of demerol was greater than a combination of one grain of codeine sulphate and 10 grains of acetylsalicylic acid.

*Pain of Gastrointestinal Origin.* Of the 22 patients in this group nine suffered from benign duodenal or gastric ulcers, 10 from carcinoma of the gastrointestinal tract, and one each from irritable bowel, uremic enterocolitis, and intestinal colic following abdominal paracentesis. In regard to the evidence for a spasmolytic action in this group, it should be stated that although an element of gastrointestinal spasm was undoubtedly present in a number of the others, the last three patients were the only ones in whom typical colic was present. Relief was complete in two of the patients. The third patient was a young woman with extremely severe cramps which were at first suspected of being due to lead poisoning, but later diagnosed as irritable bowel. She obtained no relief from 100 milligrams, and very slight relief from 200 milligrams of demerol given intramuscularly. The results in patients with peptic ulcer were uniformly good even when the ulcer was penetrating in type and accompanied by severe pain with radiation to the back or up over the anterior thoracic wall. The promptness of the effect after intramuscular injection and the failure of other measures to control the pain made it perfectly clear that demerol, rather than diet or antacids, was responsible for the symptomatic relief obtained. Variable results occurred among the patients with carcinoma of the gastrointestinal tract.

*Biliary Tract Pain.* Two of the five patients in this group had severe biliary colic. One obtained complete relief from demerol; the second, who was found at operation to have a complicating acute pancreatitis, obtained enough relief to be fairly comfortable although the physical findings over the abdomen were not obscured. One-fourth of a grain of morphine sulphate, given subsequently, produced complete relief, but also masked the abdominal findings. The difference in this case between the effects of morphine and demerol upon the physical findings is of some interest from the point of view of the diagnosis of acute abdominal conditions following the use of analgetic agents. Two other patients with less severe pain associated with acute cholecystitis were completely relieved by demerol. The fifth patient, who suffered from a dull steady pain due to primary carcinoma of the liver, was not relieved by oral medication with demerol.

*Renal Pain.* None of the patients in this group had typical severe renal colic. Four suffered from acute pyelonephritis, one from renal infarction and one from renal disease of indeterminate etiology. All obtained complete relief.

*Nerve Root or Thalamic Pain.* There were 18 patients in this group. Three suffered from severe pain of thalamic origin and each was completely relieved. Three had tabes dorsalis, and of these two were completely and one partially relieved. Four had sciatic pain and all were completely relieved. One patient with Buerger's disease and ischemic neuritis was not relieved. The remaining seven patients suffered from nerve root pain of various origin, including protruded intervertebral disc, transverse myelitis, and carcinoma with metastases to the spine or other structures adjacent to nerves. In spite of the severity of this type of pain, in the whole group 11 patients were completely relieved, six partially relieved, and only one not relieved.

A case illustrating the beneficial effect of demerol in pain of thalamic origin is that of a white male 62 years of age who suffered from hepatic cirrhosis and Parkinson's disease of arteriosclerotic origin. Very severe lancinating pains of thalamic type were present over the entire left side of his body. He had been maintained on three or four one-fourth grain doses of morphine sulphate daily. This amount controlled the pain, but the patient was depressed, "groggy," and disoriented. One hundred milligrams of demerol given orally every four hours did not give satisfactory relief, but the same amount given intramuscularly every six hours produced satisfactory relief of pain. In addition, his mental state changed to one of mild euphoria with considerable mental clearing. The sedative effect was not marked and additional medication was required for sleep.

Two other patients with so-called "intractable pain" of thalamic origin were very well controlled by oral administration of demerol for 211 and 175 days respectively.

*Pain of Osseous Origin.* In the eight cases in this group the diagnoses included several cases of metastatic carcinoma of bone, sarcoma of bone, and erosion of the spine due to aortic aneurysm. They were the group which was most resistant to demerol as well as to other analgetic drugs. Three were unrelieved, two partially relieved, and only three were completely relieved. In several instances it was found that morphine gave more relief than demerol.

*Headache.* Of the 18 patients in this group seven had headaches associated with arterial hypertension and of these, four had severe hypertension with marked retinopathy and other evidences of hypertensive encephalopathy. Other diagnoses included cavernous sinus thrombosis, meningococcic meningitis, subarachnoid hemorrhage, headache following spinal puncture, and others. In even the most severe headaches complete relief was almost always obtained. One patient with hypertensive encephalopathy required 0.2 gram for complete relief whereas the others with this condition were completely

relieved by the usual dose. Patients with less severe and less well-defined headaches were, as a rule, the ones incompletely relieved or unrelieved.

*Pleural Pain.* Eight of the 12 patients in this group suffered from pneumococcic pneumonia complicated by acute pleurisy. With one exception, complete relief from pain occurred within 10 to 15 minutes following the intramuscular injection of demerol, and sleep was induced in four patients. Respirations were slower, but not abnormally depressed. The failures occurred in patients with pleuritic pain due to pulmonary infarction associated with congestive cardiac failure.

*Cardiac Pain.* Five patients suffered from pain due to insufficiency of the coronary circulation. One such patient experienced prolonged anginal pain a few days following an acute myocardial infarction and was relieved after receiving demerol orally. Four patients suffered from repeated attacks of angina pectoris. An oral maintenance dose seemed to diminish the frequency and severity of these attacks. One of these patients was a 61 year old innkeeper with hypertensive and arteriosclerotic heart disease. During two control periods, totaling 41 days in which he received 10 grains of acetylsalicylic acid four times daily, he experienced 28 attacks of angina pectoris, whereas during two alternate periods totaling 59 days in which he received 100 milligrams of demerol four times daily, he had only 15 attacks. The patient was not aware of the nature of the drugs he received. The results in these cases of angina pectoris were suggestive, but not conclusive, of a beneficial effect of the drug. This may have been brought about either by its sedative or by its analgetic action or both. One patient was repeatedly relieved of severe pain due to acute pericarditis. Three of the remaining four patients suffered from chronic rheumatic heart disease with precordial aching pain and the last patient was diagnosed as having a cardiac neurosis.

*Miscellaneous.* Eight of the 15 patients in this group suffered from carcinoma of the bladder, or the female genital tract. Two suffered from dysmenorrhea, two from extensive dermatitis, and one each from burns, post-hemorrhoidectomy pain, and muscular pains associated with sickle-cell anemia. The results in the patients with carcinoma were variable but generally good. One patient with dysmenorrhea was completely relieved, but the other was unrelieved. Both the pain and intense pruritus present in the cases with dermatitis were completely relieved. The patient with extensive second and third degree burns was only slightly relieved.

An example of the substitution of demerol for morphine in the treatment of patients with far-advanced malignant neoplasms is the case of a 54 year old white woman who was suffering from epidermoid carcinoma of the vagina. This tumor was given a microscopical grading of 4 (on the basis of 1-4), and it had metastasized and extended until it involved practically the entire pelvis, including the rectum and bladder. She complained of constant excruciating pain in this region. One and one-half grains of codeine sulphate produced very little relief, but one-sixth of a grain of morphine sulphate given every four hours caused satisfactory relief of pain. This

dosage was continued for 107 days, following which 50 milligrams of demerol were administered every three hours for five doses in place of the morphine, which had been given during the day and two doses of morphine were continued during the night. For about seven days the patient suffered from nervousness, anorexia, nausea, vomiting, diarrhea and severe mental depression. These symptoms were thought to be caused in part by the withdrawal of morphine and were treated with frequent small doses of phenobarbital. On the eleventh day of this régime she began to feel better and soon became entirely comfortable. At no time during the transition from morphine to demerol had pain reappeared. Phenobarbital was discontinued on the sixteenth day and on the twenty-second day the nightly doses of morphine were replaced by demerol without any further withdrawal

TABLE II  
Analgetic Effect of Demerol  
(127 Instances in 81 Patients)

Degree of Pain	Results					
	Complete Relief		Partial Relief		No Relief	
	No. Instances	Group %	No. Instances	Group %	No. Instances	Group %
Group 1 Very severe (44 instances)	26	59.1%	8	18.2%	10	22.7%
Group 2 Severe (50 instances)	29	58.0%	14	28.0%	7	14.0%
Group 3 Moderately severe (33 instances)	25	75.7%	6	18.2%	2	6.1%
Combined groups (127 instances)	80	63.0%	28	22.0%	19	15.0%

symptoms. The patient remained slightly euphoric, free of pain and relatively comfortable in spite of her steady downward course. A slight sedative action was present, but additional medication was required for sleep. She died on the seventy-sixth day of demerol administration and had been well-relieved of her pain until about six days before death when it became suddenly uncontrollable by any medication. Autopsy revealed nothing suggestive of toxic effects of the drug on any of the organs.

*Analgetic Effect of Demerol in Various Grades of Pain.* Table 2 shows the results obtained in 127 separate instances of varying grades of pain experienced by 81 of the patients. In contrast to table 1 in which relief was graded from a consideration of the over-all response of the patients concerned, table 2 is composed of the results following individual doses in which the degree of pain just before the drug was administered was recorded and

the effects of the particular dose noted. Although the grading of pain is necessarily only approximate, its validity seems to be borne out by the fact that the percentage of failures was higher in the groups with what was considered to be more severe pain. The total percentages of complete, partial, and no relief are very close to those obtained by the method of analysis used in table 1. It is significant that even in the severest degrees of pain complete relief was obtained in nearly 60 per cent of instances.

### SEDATIVE EFFECTS

*Summary of the Literature.* The sedative effect of demerol in producing "pleasant drowsiness" or outright sleep frequently has been noted to amplify its analgetic action.<sup>11, 13, 14, 18, 19, 21, 26, 27</sup> The former effect, it seems, is due to a general reduction of all functions of the central nervous system, including the vomiting center. Because of the latter action demerol has been

TABLE III  
Sedative Effect of Demerol in Presence of Pain  
(99 instances in 81 patients)

Degree of Pain	Results					
	Sleep Induced		Sedation without Sleep		No Effect	
	No. Instances	Group %	No. Instances	Group %	No. Instances	Group %
Group 1 Very severe (33 instances)	18	54.5%	6	18.2%	9	27.3%
Group 2 Severe (37 instances)	15	40.5%	15	40.5%	7	19.0%
Group 3 Moderately severe (29 instances)	17	58.6%	9	31.0%	3	10.4%
Combined groups (99 instances)	50	50.5%	30	30.3%	19	19.2%

used to advantage in pneumoencephalography,<sup>33</sup> in whooping cough, and in habitual vomiting in children.<sup>12</sup> The sedative effect is not uniformly present and occasionally an increase in perceptiveness has been observed following therapeutic doses. This has resulted in anxiety and hyperexcitability<sup>21, 28</sup> or increased acuity in sensual perception similar to that observed with morphine.<sup>9, 29</sup>

*Present Study.* The sedative effects of demerol were studied in two groups of patients, one in which pain was present and the other, a smaller group of 24 patients, in which pain was absent. Table 3 shows the sedative

action in 99 instances of varying degrees of pain experienced by 81 patients. These instances were selected because the presence or absence of an effect was more clearly related to the administration of the drug than it was in others. This selection probably tends to exaggerate somewhat the favorable responses since questionable results are discarded. However, a certain degree of accuracy is indicated by the higher percentages of failures in the groups with more severe pain. Sleep was induced in from approximately 40 to 60 per cent, sedation without sleep in from about 20 to 40 per cent, and no sedative effect in from about 10 to 30 per cent of instances. The sedative effects in these patients were probably due in part to the relief from pain combined with a state of physical exhaustion incident to the illness rather than to a purely sedative action.

Twelve of the 24 patients whose illnesses were not accompanied by pain were suffering from cardiac disease with congestive failure. Among these patients sleep was induced in five, a variable effect occurred in three, no sedative effect was present in three and in one the results were indeterminate. Several patients in marked cardiac failure responded satisfactorily; however, relief was not as consistently present as when morphine sulphate was given, and this drug induced sleep in several patients not helped by demerol. Demerol seemed quite useful in two patients who were restless and disoriented during the terminal phase of uremia. They were not as deeply sedated as with morphine or barbiturates, but were quiet and slightly euphoric. Two patients with toxic delirium went to sleep promptly after intramuscular injection, and two other patients who experienced episodes of acute apprehension were similarly affected. In the entire group sleep was induced in 11, a sedative effect without sleep in four, no effect in three, a variable effect in three, and an indeterminate effect in three patients.

### BRONCHIAL ASTHMA

Four patients with bronchial asthma were given demerol. One patient who failed to respond to epinephrine or rectal ether anesthesia obtained definite relief following demerol with induction of sleep within about 20 minutes. A second patient had obtained no relief from epinephrine given as a spray and subcutaneously or from aminophylline given intravenously. The dyspnea persisted during the first four days of hospitalization during which demerol gave satisfactory relief lasting for varying periods. The third patient had also obtained no relief from epinephrine or aminophylline. The first dose of demerol gave no relief but two days later the next and several subsequent doses were effective. It is probable that both sedative and antispasmodic actions were operative in these cases. The fourth patient had only moderately severe asthma and was admitted to the hospital chiefly because of acute cystitis with marked dysuria. Demerol gave no relief from either symptom on two occasions.



## SIDE-EFFECTS

*Summary of the Literature.* Demerol in therapeutic dosage may produce a number of reactions not sedative or analgetic in character. These, it is claimed, were rarely marked and seldom interfered seriously with its use. The most common side-reactions mentioned are dizziness and sweating,<sup>14, 20, 21, 26, 27, 28, 29, 34</sup> nausea with or without vomiting, and vomiting without nausea.<sup>14, 16, 19, 21, 27</sup> Euphoria,<sup>14, 15, 33</sup> headache, anxiety and oppression are occasionally observed.<sup>28, 29, 34</sup> Intravenous injection has been claimed to cause a slight drop in systolic and diastolic blood pressure.<sup>11, 30</sup> Increase of respiratory and basal metabolic rates, lowering of glucose tolerance and decrease of gastric secretion in man have been noted.<sup>20</sup>

TABLE IV  
Side-Effects of Demerol  
(Experienced by 40 of 146 Patients)

Symptoms	No. of Instances
Subjective vertigo.....	10 (1)*
Induration of tissues at site of injection.....	10
Dryness of mouth.....	10
Euphoria.....	8
Nausea + vomiting.....	5 (3)
Paresthesias.....	4
Nausea.....	3
Sweating.....	2
Muscular relaxation.....	2
Palpitation and increased dyspnea.....	1 (1)
Vascular collapse with bronchial spasm.....	1 (1)
Insomnia and restlessness.....	1 (1)
Transient dimness of vision, pain at site of injection, drug eruption (?), delusions, urticaria—each.....	1
	<hr/> 67 (7)

\* Numbers in parentheses indicate cases in which side-effects necessitated stopping demerol.

*Present Study.* Table 4 summarizes the side-effects experienced by 40 individuals, who constitute 27.4 per cent of the total number of patients in our series. Since some patients noticed two or more of these symptoms the number of instances exceeds the number of patients. In only seven patients, or 4.8 per cent of the series were these effects sufficiently severe to require stopping the drug. With one exception the vertigo was mild and frequently preceded sleep by only a few minutes. Induration at the site of injection was noticed chiefly in patients who had received the drug several times daily for more than one month. It consisted of a firm, leathery, non-tender induration of the skin, subcutaneous tissues, and possibly underlying muscle. Also small subcutaneous hemorrhages which gave the area a bruised appearance were present in most of these cases. These changes were discovered late in the course of the study and thereafter, when carefully looked for, were seen in nine of 11 patients. Similar changes have not been

reported previously and it is possible that they resulted from the inadvertent injection of the drug into the subcutaneous tissues.

The euphoria was mild, perhaps better described as an "attitude of non-chalance." Nausea and vomiting occurred in five patients and was severe enough to require stopping the drug in three. Three other patients had nausea only. Palpitation and increased dyspnea followed each of two intramuscular injections given to a patient suffering from chronic rheumatic heart disease with congestive failure. A similar reaction was not seen in a number of other patients with heart disease. Another patient had received 100 milligrams of demerol intramuscularly from three to four times daily without any side-effects and with good relief of his lancinating tabetic pain. On the twenty-fifth day demerol was discontinued and replaced by one-grain doses of codeine. This was continued for 34 days when demerol was readministered intramuscularly in doses of 100 milligrams. The first dose was well tolerated. The second was followed by severe vasomotor collapse, bronchial spasm, nausea and vomiting. Subsequently these symptoms were reproduced on two occasions. Twenty-five milligrams of demerol caused no untoward symptoms but did not give the desired relief of pain. The occurrence of these reactions upon readministration of demerol suggests the possibility of some type of hypersensitivity in this patient. One patient was made increasingly restless and wakeful. In general, it should be emphasized that the incidence of serious side-effects was low.

### TOXIC EFFECTS

*Summary of the Literature.* When demerol is given in doses of 100 milligrams or more from 10 to 20 times daily, certain reactions occur which must be interpreted as due to direct toxic effects of the drug. Many of the reported cases showed signs comparable to atropine or hyoscine poisoning, characterized by maximal dilatation of the ocular pupils, severe excitation, hallucination, disorientation as to time and place, muscular twitches and jerks, dryness of the mouth, tachycardia, disturbances in smell and taste and cold sensations.<sup>34, 36, 37</sup> In a carefully controlled study of drug addicts who received demerol in doses ranging from 825 to 2985 milligrams daily for from 10 to 11 weeks, Himmelsbach<sup>8</sup> demonstrated slight rises in blood pressure, pulse rate and temperature. Muscular tremors and twitches appeared in the second week. Reflexes became hyperactive and stimuli ordinarily not disturbing were found to cause an excessive response. One patient developed a "mild toxic psychosis" and two were claimed to have petit mal seizures during the tenth week. One patient reported by Kucher<sup>37</sup> experienced a frank epileptiform seizure following overdosage of demerol; however, this patient also had been taking "Phanodorm" for a considerable period of time. Using the same group of patients as Himmelsbach, Andrews<sup>10</sup> reported the results of electroencephalographic examinations. These revealed abnormal records with an increase in the percentage of low frequency

(delta) waves. In general, the electroencephalographic changes were much more marked than those occurring after large doses of morphine and indicated "a profound effect on the central nervous system when used in quantities sufficient to satisfy the desires of addicts." This pattern differed significantly from that observed in addicts under the influence of codeine or morphine whose records showed an increase in voltage with decrease in the frequency of the basic (alpha) rhythm.<sup>38</sup> No significant changes have ever been observed in routine laboratory tests or in serial electrocardiograms.

*Present Study.* None of our patients received doses comparable with those cited above. This may account for the absence of "toxic" reactions of the types described. The laboratory findings in both the larger group of patients and the group of 26 patients for whom these tests were repeated at regular intervals did not show any changes which could be interpreted as being due to demerol.

### ADDICTION

In 1938 the Committee on Drug Addiction of the National Research Council stated that it had not been possible "... to prepare a drug with the power to control pain requisite for a morphine substitute without at the same time introducing factors which cause the appearance of other phenomena leading to addiction."<sup>39</sup> This statement referred to all substances derived from opium directly or obtained by altering the structure of the morphine molecule. Most analgetics of this type at one time or another have been claimed not to be habit forming. This was true of heroin,<sup>40</sup> dilaudid,<sup>41</sup> and codeine.<sup>38</sup>

Structural similarities between morphine and demerol have been considered previously.<sup>1</sup> Demerol also has been claimed not to be habit forming,<sup>14, 17, 18, 22, 26, 27</sup> but a few cases suggestive of addiction have been reported.<sup>19, 35, 36, 37, 42, 43</sup> In all of these cases withdrawal symptoms were present following periods of excessive dosage and all cases observed were either those of severely psychopathic patients or former morphine addicts. "Typical withdrawal symptoms" occurred, but they were milder and easier to overcome than those with morphine. Recently Himmelsbach (in the study mentioned above under "toxic effects") reported on the addiction liability of demerol.<sup>8</sup> Again, these subjects were former morphine addicts. All developed the triad of tolerance, habituation and dependence requisite for the diagnosis of addiction.<sup>39</sup> The doses were excessive and symptoms of withdrawal were mild. The same subjects were studied by Andrews<sup>9</sup> for the development of tolerance. He stated that "The tolerance developed to demerol is maintained beyond the period of administration but appears to be less permanent than that developed to morphine." It must be stressed that so-called "primary addiction" following ordinary therapeutic dosages has not been reported. Thus Batterman<sup>3</sup> found no instances of primary addiction among his patients receiving the drug in controlled doses for several weeks

or months, but noted a few cases in which a desire for the drug was expressed. He stated that habituation, as distinguished from addiction, may be produced by demerol and that the possibility of the occurrence of addiction after extended administration in patients with chronic illness had not been excluded. Demerol has been placed under the narcotic law in Germany.<sup>44</sup>

The group of 26 patients who received demerol for the relief of pain over a considerable period of time was not well suited for a study on tolerance, habituation and dependence.

Tolerance, a gradual decrease in the effectiveness of a given dose produced by repeated administration of a drug, may have been present in nine of the patients of this group for whom the dosage of the drug had to be increased from time to time, but in only one was it certain that the need for larger amounts was not due to an increase in the intensity of the pain.

Habituation, or "mental conditioning to the repetition of an effect,"<sup>39</sup> could not be tested since the patients required an analgetic at all times and were in acute discomfort when they did not receive it. On occasions when an injection of saline was substituted the patients invariably complained of severe pain.

Dependence is determined by the appearance of certain signs and symptoms upon withdrawal of a drug. It was thought that dependence could not be tested in our patients since opiates had to be substituted immediately upon withholding demerol and thus might have masked any symptoms of withdrawal.

TABLE V  
Symptoms Following Withdrawal of Demerol in Nine Persons

Periods of Demerol Administration (in Days)							
	1-10	11-20	21-30	31-40	41-50	51-60	Over 60
Drug addiction*	0 (s)	+++ (s)					
Ca. of tongue			+	(c)			
Peripheral neuritis			+	(c)			
Ca. of bladder		+	(c)		+++ (m)		
Ca. of breast		+++ (c)	+++ (d)		++ (c)		
Ca. of cervix	0 (s)			++ (c) ++ (c)		++ (c)	
Subacute bacterial endocarditis					++++ (c)		
Transverse myelitis					+	(m)	+++ (m)
Ca. of tongue*							++ (m) +++ (d) 66th day +++ (m) 100th day +++ (d) 120th day +++ (d) 170th day

\* See text.  
s saline injection  
c codeine  
d dilaudid  
m morphine  
} used as substitutes

0 no reaction  
+ opiates ineffective for several hours  
++ nausea, vomiting, sweating  
+++ nausea, vomiting, irritation, nervousness  
++++ nausea, vomiting, irritation, nervousness, itching of skin

However, among 21 patients from whom demerol was withdrawn a total of 38 times there were nine who developed reactions of varying intensity (table 5). In eight of the patients demerol was replaced by one of the opiates and in one patient no medication was given. The reactions seen on withdrawal of demerol consisted of nausea, vomiting, perspiration, jerking and tremor of muscles, nervousness, irritation, depression and itching of the skin. The symptoms usually began several hours after the last injection of demerol and one or two hours after the first injection of opiates which were substituted without the patient's knowledge. They usually lasted for 12 to 24 hours, occasionally for 48 hours, and were readily controlled by the administration of barbiturates and hyoscine. There appeared to be a higher incidence of these symptoms in patients who had received demerol for a longer period of time. This is indicated by the fact that in the total group of 21 patients only six of the 19 withdrawals before the thirtieth day but 12 of 13 withdrawals after 30 days were followed by symptoms. In three patients who received demerol orally withdrawal at various intervals up to 211 days was not followed by any untoward reactions.

The only patient (first case in table 5) in whom opiates were not substituted after withdrawal of demerol was a 36 year old American nurse complaining of severe low back pain. This pain was found to be caused by a protruded intervertebral disc which had been present for several years and had led to morphine and codeine addiction. However, she had not been taking opiates in any form for several months prior to entering the hospital. When demerol was administered it afforded immediate and complete relief which lasted for three hours following each injection of 100 milligrams. Some nausea and vomiting were noted following the first injections. The first withdrawal of demerol on the second day (replaced by sterile saline injections) was followed by prompt return of pain. During the second week of administration the patient noticed restlessness, depression and a feeling of anticipation about one hour before the next injection was "due." This she described as "craving" and recognized it as being similar in type to the sensation she had experienced during morphine addiction. On the fourteenth day of treatment the drug was replaced by sterile saline injections. The last injection of demerol was given at seven o'clock in the morning and four hours later she began to perspire freely, noticed jerking of her muscles, and became quite apprehensive. One hour after this, the pain returned and the patient became extremely depressed and agitated and felt herself "abused." She cried vehemently, was nauseated, and vomited profusely. All these signs increased to an alarming degree until two o'clock in the afternoon when hyoscine and phenobarbital were administered. During the afternoon she gradually became calm and except for pain was relatively comfortable the next morning.

In this case the reaction could not possibly be attributed to opiates since none was administered. The appearance of these symptoms after only two

weeks of demerol administration is unusual and could perhaps be explained partially as a psychologic response to the return of pain.

A representative case, in which reactions of this type were observed while pain was adequately controlled, is that of a 61 year old American bartender who suffered from carcinoma of the tongue with regional metastases. For months he had complained of intense pain in his mouth, neck and face which was not appreciably altered by several courses of roentgen and radium therapy. During a period of 27 days morphine sulphate in one-quarter grain doses every four hours gave good relief from the pain and produced no ill effects. Then morphine was withdrawn and demerol substituted. The only symptoms suggestive of morphine withdrawal which the patient experienced at this time were insomnia and slight restlessness. These symptoms persisted for only a few days and disappeared following the administration of phenobarbital. Relief of pain lasted for two or three hours, but was not as complete as with morphine. On the sixty-sixth day of treatment at two o'clock in the afternoon demerol was replaced by morphine in one-sixth grain doses. Later in the day the patient became nauseated and restless. The next morning severe vomiting occurred and was associated with pronounced hyperhidrosis and fine tremor of the extremities. This seemed to be aggravated by each morphine injection although these had been well tolerated before. Pain was controlled throughout and the patient began to feel well again on the afternoon of the second day. Three days later demerol was again substituted for morphine without the appearance of any untoward symptoms. On the one hundredth day demerol was withdrawn a second time. The last dose of demerol was given at six o'clock in the morning and one-twentieth grain of dilaudid which the patient had tolerated well at other times was substituted from nine o'clock on. At 11 o'clock the patient complained of severe nausea and vomited several times during the rest of the day. He spent a fair night but the next morning began to experience increased nervousness, perspiration, muscular tremors, and an intense itching of the skin. At noon he vomited several times and became extremely depressed and agitated. Demerol was administered and all symptoms subsided within one hour. A third withdrawal of demerol on the one hundred twentieth day with morphine as the substitute and a fourth on the one hundred seventieth day using dilaudid were followed by almost identical reactions. On the latter occasion administration of sodium amytal and hyoscine was necessary during the first day. All signs and symptoms abated on the second day following withdrawal of demerol.

The reactions observed were undoubtedly related to the withdrawal of demerol. They may have been influenced or intensified by opiates given during the withdrawal period. This is suggested by the usual appearance of the symptoms one or two hours after their administration. On the other hand five of these patients had received either morphine or codeine prior to demerol administration and had not shown any signs of intolerance. Hence it is difficult to evaluate the rôle the opiates may have played. Further, the

fact that these reactions were not prevented by either morphine or dilaudid, drugs which might be expected to satisfy dependence needs, complicates the interpretation of these symptoms as part of an abstinence syndrome. Also, the early appearance of nausea and vomiting and the absence of yawning, lacrimation, rhinorrhea, etc.,<sup>8</sup> are not characteristic of the picture seen following withdrawal of morphine. However, the circumstances under which these reactions occurred suggest the possibility that addiction to demerol may have been present. Further studies concerning the addicting properties of demerol in subjects who do not require additional medication for the relief of pain and who have no previous history of habituation or dependence on other drugs seem definitely to be indicated.

### SUMMARY AND CONCLUSIONS

1. In 123 instances of severe pain occurring among 118 patients complete relief followed the administration of demerol in 79 (64.2 per cent), partial relief in 29 (23.6 per cent), and no relief in 15 (12.2 per cent). The customary dose was 100 milligrams given orally or intramuscularly.

2. The onset of relief was from five to 20 minutes following intramuscular injection, and from 20 to 30 minutes following oral administration. Its duration varied between one and six hours, but was usually three or four hours. Relief was more often complete following intramuscular injection.

3. The analgetic potency of demerol in the dose employed was greater than that of one grain or more of codeine, or combinations of codeine and aspirin. It was usually less than that of morphine in one-quarter or one-sixth grain doses.

4. The sedative action of demerol was studied in the group of 81 patients with pain and in 24 patients without pain. The group of patients with pain received, as a rule, only a few doses of demerol. Its administration was followed by sleep in about 50 per cent, by mild sedation in about 30 per cent, and by no noticeable sedative effect in about 20 per cent of instances. The hypnotic or sedative effects following repeated administration were not profound, a fact which was of advantage in the treatment of patients with chronic painful diseases.

5. Three patients suffering from status asthmaticus were benefited by demerol, although a fourth asthmatic patient was not.

6. Side effects were noted by 40 (27.4 per cent) of the 146 patients, but in only seven (4.8 per cent) was it necessary to stop the drug. Two patients developed reactions which were somewhat alarming.

7. Laboratory studies showed no changes which could be attributed to demerol, although the drug was given at regular intervals for as long as 211 consecutive days and 26 patients received an average total dose of 32.6 grams.

8. In nine of 21 patients who had received demerol for varying periods of time the withdrawal of the drug and the substitution of one of the opiates

were followed by certain undesirable symptoms, the significance of which is discussed.

9. It is concluded that demerol is an effective analgetic drug which is relatively non-toxic. It may possess addictive properties but these are apparently not as marked as those of some of the opiates, morphine and its derivatives. It may be said that demerol is capable of replacing these drugs in a great number of painful conditions.

# BIBLIOGRAPHY

1. YONKMAN, F. F., NOTH, P. H., and HECHT, H. H.: Demerol, a new synthetic analgetic, spasmolytic and sedative agent. I. Pharmacological observations, *ANN. INT. MED.*, 1944, xxi, 7-16.
2. HECHT, H. H., NOTH, P. H., and YONKMAN, F. F.: Demerol, clinical observations, *Jr. Am. Med. Assoc.*, 1943; cxxi, 1307.
3. BATTERMAN, R. C.: The clinical effectiveness and safety of a new synthetic analgesic drug, demerol, *Arch. Int. Med.*, 1943, lxxi, 345.
4. ROVENSTINE, E. A., and BATTERMAN, R. C.: The utility of demerol as a substitute for opiates in preanesthetic medication, *Anesthesiology*, 1943, iv, 126.
5. BATTERMAN, R. C., and MULHOLLAND, J. H.: Demerol, a substitute for morphine in the treatment of postoperative pain, *Arch. Surg.*, 1943, xlv, 404.
6. GILBERT, GORDON, and DIXON, A. B.: Observations on demerol as an obstetric analgesic, *Am. Jr. Obst. and Gynec.*, 1943, xlv, 320.
7. ROBY, C., and SCHUMANN, W. R.: Demerol (S-140) and scopolamine in labor: a preliminary report, *Am. Jr. Obst. and Gynec.*, 1943, xlv, 318.
8. HIMMELSBACH, C. K.: Studies on the addiction liability of "Demerol" (D 140), *Jr. Pharmacol. and Exper. Therap.*, 1942, lxxv, 64-68.
9. ANDREWS, H. L.: The development of tolerance to demerol, *Jr. Pharmacol. and Exper. Therap.*, 1942, lxxv, 338.
10. ANDREWS, H. L.: Cortical effects of demerol, *Jr. Pharmacol. and Exper. Therap.*, 1942, lxxvi, 89-94.
11. GARCIA-HUIDOBRO, M.: Ensayo de un nueva anelgésico en el respedo uterino, *Bol. de la Soc. Chil. de obst. y gin.*, 1941, vi, 371.
12. SPROCKHOFF, O.: Dolantin in der Kinderheilkunde, *Deutsch. med. Wchnschr.*, 1941, lxvii, 383.
13. BENTHIN, W.: Schmerzlinderung in der Geburt durch Dolantin, *Deutsch. med. Wchnschr.*, 1940, lxvi, 760-762.
14. DIETRICH, H.: Klinische Erfahrungen mit einem neuen synthetischen Spasmolyticum und Analgeticum, *Deutsch. med. Wchnschr.*, 1939, lxv, 969-970.
15. KLEIN, E. K.: Erfahrungen mit Dolantin, einem myotrop und neurotrop wirkendem Spasmolyticum, *München. med. Wchnschr.*, 1939, ii, 1676.
16. VOGT, K. E.: Dolantin zur Schmerzbekämpfung bei inneren Erkrankungen, *Med. Klin.*, 1940, xxiii, 622.
17. ERLÉNDSOON, V.: Dolantin "Bayer," *Ugesk. f. Læger*, 1940, cii, 1330-1331.
18. SCHIPLER, V.: Dolantin, *Ugesk. f. Læger*, 1940, cii, 1328-1330.
19. GARDA, D.: El uso clínico de la Dolantina y su abuso por los toxicomanos, *Día méd.*, 1941, xiii, 1053-1054.
20. IZAR, G., and LENZI, S.: Studi sulla Dolantin, *Rassegna internaz. di clin. e terap.*, 1941, xxii, 215-221, 251-256.
21. HEYDNER, W.: Erfahrungen mit dem Spasmo-analgeticum Dolantin bei Herzkranken, *Fortschr. d. Therap.*, 1940, xvi, 33.



22. ALTHOFF, H.: Klinische Erfahrungen mit Dolantin Bayer, *Ther. d. Gegenwart*, 1939, lxxx, 259.
23. SCHLUNGBAUM, H.: Schmerzbekämpfung mit Dolantin, einem synthetisch hergestellten Spasmolytikum und Analgetikum, *Med. Klin.*, 1939, xxxv, 1259.
24. GRIGORESCU: Dolantin in terapeutică durerii, *România med.*, 1941, xix, 27.
25. SÁNDOR, D., and GYÖRGY, S.: Klinikai tapasztalatok a Dolantinual az ideggyógyászatban, *Gyógyászat*, 1941, xx, 289.
26. ROSENTHAL, H.: Beobachtungen zur Bekämpfung des Wundschmerzes mit dem neuen Analgeticum Dolantin, München. med. Wchnschr., 1939, lxxxvi, 1079-1080.
27. SCHÄFER, F.: Schmerzbekämpfung in der Chirurgie mit Dolantin, *Deutsch. med. Wchnschr.*, 1939, lxxv, 970-972.
28. REISINGER, F.: Das neue Analgeticum und Spasmolyticum Dolantin, *Wien. med. Wchnschr.*, 1940, xc, 400.
29. DOLLE, W.: Dolantin, ein neues Spasmolyticum und Analgeticum in der Gynäkologie, *Der prakt. Arzt*, 1940, xxv, 113.
30. SOSTMAN, A.: Zur Ablösung des Morphin und seiner Abkömmlinge in der Gynäkologie durch Dolantin, *Med. Welt*, 1940, xiv, 325.
31. SONNEK, W.: Geburtserleichterung durch Dolantin, *Deutsch. med. Wchnschr.*, 1941, lxxvii, 868-871.
32. JESSEN, H.: Dolantin in recurrent hiccups, *Jr. Am. Med. Assoc.*, 1942, cxviii, 674.
33. JESSEN, H.: Om Dolantin, *Ugesk. f. Læger*, 1940, cii, 1326-1328.
34. WERNER, A.: Zur Behandlung der multiplen Sclerose, *Psychiat.-neurol. Wchnschr.*, 1939, xli, 441.
35. WILPERT, H.: Das neue Spasmolyticum Dolantin, *Tung Chi med. Monatsschr.*, 1941, xvi, i, 33.
36. VON BRÜCKE, S.: Über Dolantin Abusus und einen Fall von Dolantindelir., *Wien. klin. Wchnschr.*, 1940, liii, 854-856.
37. KUCHER, I.: Zwei Fälle von Dolantinsucht, *Klin. Wchnschr.*, 1940, xix, 688-689.
38. HIMMELSBACH, C. K., ANDREWS, H. L., FELIX, R. H., OBERST, F. W., and DAVENPORT, L. F.: Studies on codein addiction, *Pub. Health Rep., U. S. Government printing office*, 1940, Supplement CLVIII.
39. SMALL, L. F., EDDY, N. B., MOSETTIG, E., and HIMMELSBACH, C. K.: Studies on drug addiction, *Pub. Health Rep., U. S. Government printing office*, 1938, Supplement CXXXVIII.
40. TERRY, C. E.: The opium problem, *Bureau of Social Hygiene, New York*, 1928.
41. KING, M. R., HIMMELSBACH, C. K., and SANDERS, R. S.: Dilaudid (Dihydromorphinone): A review of the literature and a study of its addictive properties, *Pub. Health Rep., U. S. Government printing office*, 1935, Supplement CXIII.
42. ROJAS, N., and BELBEY, J.: Hábito tóxico y dolantina, *Semana med.*, 1941, ii, 616-618.
43. SCHWARKE, R.: Addiction to dolantin, *Deutsch. Ztschr. f. d. ges. gerichtl. Med.*, 1941, xxv, 17-23.
44. *Foreign Medical News, Jr. Am. Med. Assoc.*, 1942, cxix, 1518.

## SERUM AMYLASE IN MUMPS \*

By I. L. APPLEBAUM, LIEUTENANT COLONEL, M.C., A.U.S., F.A.C.P.,  
*Ancon, Canal Zone*

THIS study was inadvertently instituted when high levels of serum amylase were noted in several cases of epidemic parotitis, utilized as controls for mumps complicated by pancreatitis. In this latter group a marked increase of serum amylase was expected. A review of the American literature of the past two decades uncovered no specific study or detailed analysis. The literature was, of course, voluminous with articles dealing with the test, its variations and its relationship to disease. Acute pancreatitis was the outstanding condition in which a high level was clinically significant. However, the tests were performed in a great variety of pathological lesions. Lewison<sup>1</sup> contributed a clinical article of interest and discussed a variety of conditions. Elman,<sup>2</sup> Popper,<sup>3</sup> Comfort,<sup>4</sup> McCorkle,<sup>5</sup> and others demonstrated its value in pancreatitis. Special studies have been made in such diverse diseases as rabies,<sup>6</sup> thyroid activity,<sup>7</sup> diabetes,<sup>8</sup> shock,<sup>9</sup> diseases of the brain,<sup>10</sup> liver disturbances,<sup>11</sup> bacterial infection,<sup>12</sup> parturition,<sup>13</sup> tuberculosis,<sup>14</sup> chronic alcoholism,<sup>15</sup> etc.

Among the many publications there were several references to increased levels in mumps. A brief report was submitted by Lewison,<sup>1</sup> who devoted a short paragraph, unattended by statistics, in a general article on the clinical value of the serum amylase test. He observed 12 instances of epidemic mumps. Bodansky and Bodansky<sup>16</sup> quote the work of Brinck and Gülzow, who noted increased levels in every one of nine cases which they investigated. Branisteanu and Boutroux<sup>17</sup> reported elevated values in a general study. Specific references were found in foreign literature. Dunlop,<sup>18</sup> in 1933, and Hershhorn<sup>19</sup> et al., in 1931, contributed brief reports. It is not within the realm of this presentation to elaborate upon the general historical background. Reference can be made to such notable contributors as Bernard,<sup>20</sup> Foster,<sup>21</sup> Wohlgemuth,<sup>22</sup> Davison,<sup>23</sup> Elman,<sup>24</sup> Muhlfield,<sup>25</sup> Somogyi<sup>26</sup> and many others.

The chief sources of this digestive enzyme are the pancreas and the salivary glands, particularly the parotid. A brief description of the histopathology and the secretions of the salivary glands furnishes a basis for better understanding. The secretions of the parotid and submaxillary glands can be obtained separately by inserting a canula in the openings of the ducts in the mouth or, according to the method of Pavlov, by transferring the end of the duct so that it opens upon the skin, thus creating a salivary fistula. Examination of the separate secretions shows that the main difference lies in the fact that the parotid saliva contains no mucin, whereas the submaxillary

\* Presented before the Medical Society of the Isthmian Canal Zone, March 16, 1943. Received for publication April 21, 1943.

From the Medical Service of Gorgas Hospital, Ancon, Canal Zone.

and especially the sublingual glands are rich in mucin. The parotid saliva of man is particularly rich in ptyalin (salivary amylase) as compared to the other glands. Thus, the parotid is described as a typical serous gland and is the chief source of the starch-splitting enzyme; the submaxillary is a mixed type; and in the sublingual glands mucous cells predominate.

The precise pathological changes of the parotid glands in mumps are still controversial, as opportunities for examination are rare. From existing evidence it would appear that the gland substance is the seat of intense hyperemia and edema, with serous and cellular infiltration of the interstitial and interglandular tissue, as well as edema of the bordering extraglandular soft tissue. A catarrhal inflammation of the ducts and their branches, which contain in their lumina desquamated epithelium and round cells, has also been observed.

Any mechanical obstruction producing retrograde passage into the lymph and blood streams, liberation of diastase \* as a result of acute damage to the parenchymatous cells secreting the enzyme, or hypersecretion will all tend to induce increased content in the blood. These factors are at play during parotid involvement in epidemic mumps, and blockage assumes a very important rôle. As a matter of fact, appreciable increases in the diastase level were observed in cases of calculous obstruction<sup>27</sup> to the salivary duct. The objective findings of inflammation and edema causing stenosis of the external orifice and swelling of the parotid gland proper have been noted since the early description of the disease, and harmonize in principle with the physiopathological concept for the abnormally high serum amylase results.

#### METHOD

The procedure employed was the determination of blood diastase by the saccharogenic action method of Somogyi as described by Gradwohl<sup>28</sup> in his textbook. The only modification was the last step, where the Folin-Wu copper reduction process was substituted for the method employed by Somogyi in the determination of the reducing sugar. The results were expressed in terms of milligrams of glucose per 100 c.c of plasma. No claim is made for precise quantitative accuracy, as the possibility of sources of error is well recognized. The following quotation from Lewison<sup>1</sup> is completely sponsored: "Technical variation has inevitably been responsible for some dissension among observers; yet if serum amylase values are regarded only with comparative and not quantitative accuracy, this reliability assumes a new importance and may well satisfy a most helpful diagnostic rôle. A lack of ultimate quantitative precision should not impugn the clinical value of the serum amylase test." The test was performed at Gorgas Hospital by the same personnel in a constant manner, so that the comparative figures can be considered of definite value.

\* Diastase and amylase are employed as interchangeable terms.

## CONTROL GROUP

This group was chosen at random from patients of various wards. Table 1 reveals an analysis of 65 consecutive cases:

TABLE I  
Serum Amylase Levels in Control Series of 65 Cases

Diagnosis	No. of Cases	Average Serum Amylase (mg. per 100 c.c.)
1. Acute appendicitis.....	2	66
2. Acute cholecystitis.....	9	59
3. Diabetes mellitus.....	4	51
4. Fever of unknown origin.....	4	68
5. Acute gastritis.....	4	48
6. Gastroenteritis.....	3	53
7. Malaria.....	3	52
8. Miscellaneous conditions.....	18	55
9. Psychoneurosis.....	3	58
10. Acute pancreatitis.....	14	281
11. Intestinal obstruction; possible pancreatitis...	1	303

There were 14 cases of pancreatitis and one possible pancreatitis exhibiting high levels. Excluding these, the average of the remaining 50 with a wide range of disease was calculated as 56.4 mg. The minimal figures were 15 and 16, noted respectively in carcinoma of the liver and cholecystitis with hepatic damage. The maximum was 117 in acute cholecystitis. Gradwohl<sup>28</sup> places the normal range between 80 and 150. As the average in this series was 56.4 and it was felt that no rigid mathematical restrictions should be imposed the range of 40-175 was adopted as the normal limits for this study.

## MATERIAL

Sixty (60) consecutive patients who were admitted to the Isolation Section of Gorgas Hospital with a diagnosis of mumps served as the source of this study. There were 95 per cent (57) adults and 5 per cent (three) children. The average age was 24 years. There were 88 per cent (53) males and 12 per cent (seven) females. The negro race comprised 67 per cent of the entire group and the white race 33 per cent. Therefore, the representative individual dominant in this group was a negro, male, young adult.

## RESULTS

In table 2 the results of serum amylase findings in various subgroups of mumps are recorded. Of the 60 cases admitted as mumps, seven were ill from other causes and three had mild unilateral involvement which completely subsided at the time blood was drawn for chemical analysis. Of the 50 remaining cases, the average serum amylase, calculated during the active stage of the disease, was 502 mg., which is almost 10 times greater

TABLE II

Serum Amylase Levels in 60 Consecutive Cases Admitted with Diagnosis of Mumps

Diagnosis	No. of Cases	Average Serum Amylase (mg. per 100 c.c.)
1. Clinical Cases of Mumps with Elevated Levels		
a. Unilateral parotitis		
(1) Without extension.....	17	392
(2) Extension to submaxillary and/or sublingual.....	4	494
b. Bilateral parotitis		
(1) Without extension.....	7	811
(2) Extraparotid salivary extension.....	9	642
c. Extraparotid salivary disease		
(1) Submaxillary gland.....	2	68
(2) Sublingual glands.....	1	127
d. Parotitis complicated by orchitis, encephalitis, etc.		
(1) Unilateral.....	2	325
(2) Bilateral.....	6	684
2. Epidemic Parotitis with Normal Levels		
a. Unilateral—completely subsided.....	3	107
b. Bilateral—active phase.....	2	95
3. Cases Admitted as Mumps, but Later Clinically Disproved		
a. Secondary lymphadenopathy, pre-auricular and cervical.....	4	83
b. Cellulitis of face secondary to infection of teeth.....	3	73

than the average of the control series. The average for bilateral involvement was 707 mg. compared to 421 mg. when a unilateral infection was present. When the disease of the salivary glands was exclusively extraparotid, as in two cases of submaxillary inflammation and one of sublingual, the results were normal. The results of the seven cases admitted as mumps

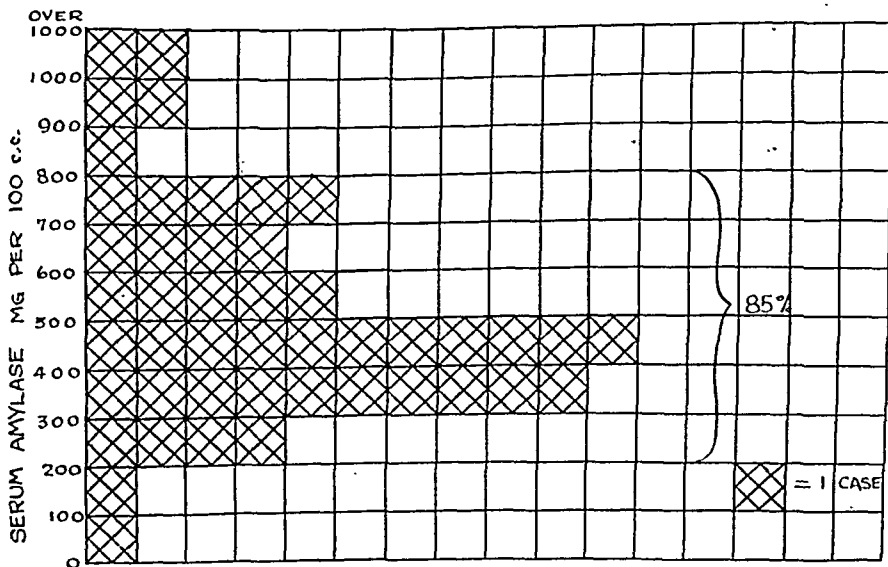


FIG. 1. Serum amylase levels in epidemic parotitis.

but proved by further observation and study to fall into another category were also normal, as were the three unilateral cases, which were discarded in the final analysis because of the tardiness of the studies. However, there were two bilateral cases, typical of mumps, presenting normal levels for which no explanation can be offered. They fell in an older age group that seemed to show lower trends. Therefore, of 47 cases of active parotid involvement, normal figures were demonstrated in only two. Markedly ele-

TABLE III  
Relationship of Reaction of Orifice of Stenson's Duct to Serum Amylase Level

Reaction (Orifice)	No. of Cases	Average Amylase (mg. per 100 c.c.)
0 (negative).....	6	269
± (mild).....	12	416
+ (moderate).....	22	584
++ (severe).....	5	737

vated levels occurred in 95 per cent. The two highest, 1297 mg. and 1852 mg., were detected in bilateral cases. Extrasalivary complications of mumps did not seem to alter results, nor did extension to extraparotid salivary glands.

Figure 1 represents a compilation of diastase levels during the active phase of parotitis (47) cases.

An attempt was made to correlate the elevation of the serum diastase with the degree of edema and inflammation around the orifice of Stenson's duct.

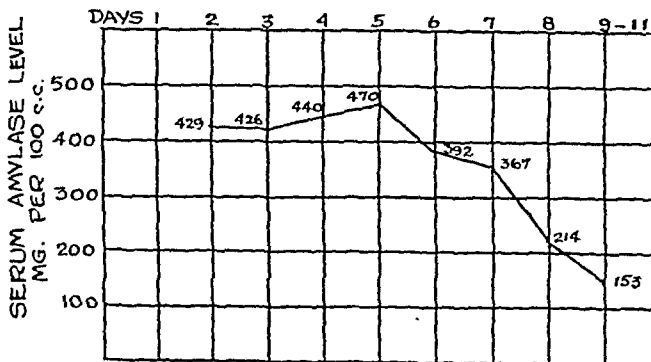


FIG. 2. Relationship of day of disease to serum amylase level in unilateral parotitis.

This reaction was expressed as 0 (none), ± (mild), + (moderate) and ++ (severe). Table 3 records these findings in 45 cases, for which accurate data were available.

The trend suggests the possibility that the more severe the reaction around the orifice, producing obstruction, the higher the level. However, the sample is small, in several cases there was a marked discrepancy, and it is possible for the duct proper to be blocked without apparent reaction at the orifice.

The relationship of the day of the disease from onset to the diastase level was studied in both unilateral and bilateral parotitis. Daily serial determinations were not made on each case and a cross section of the entire series was analyzed. In bilateral states, the day was recorded from the time both glands were involved. Some cases had several levels and others had only one, with chronological data usually based on history. Figure 2 (unilateral) and figure 3 (bilateral) reveal the average amylase level in relationship to the day of the disease.

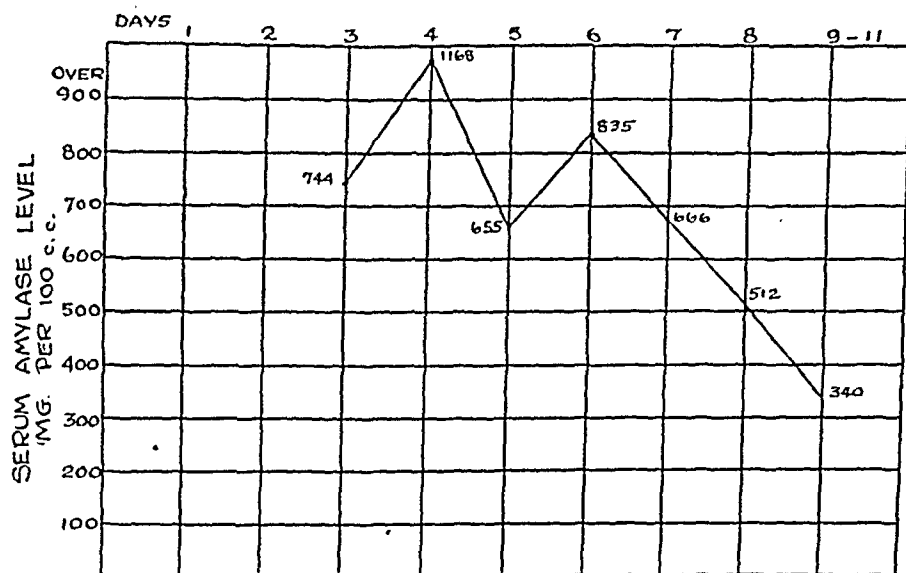


FIG. 3. Relationship of day of disease to serum amylase level in bilateral parotitis.

No conclusions can be drawn as the method is open to criticism and the sample is inadequate. However, the curves suggest that the serum amylase level is high early in the disease, that it is maintained for a week or more during the active phase, and subsides gradually with the disappearance of the swelling. In the cases of bilateral parotitis, the curve reaches a higher level and seems to be maintained over a longer period than in unilateral cases.

#### COMMENT

On the basis of these studies one cannot avoid the conclusion that an elevation of serum amylase is present in the great majority of cases of epidemic mumps. It is especially to be expected since the parotid gland which is the chief salivary enzyme producer is frequently affected. The finding is naturally of academic interest and has a sound basis. Although the diagnosis of mumps is usually simple, there are cases which present differential problems. In this series of 60, there were seven patients who presented clinically suspicious findings and had positive contact histories. The normal serum amylase helped to rule out contagion and the subsequent course and objective findings confirmed the reliability of this test. Elevated levels also

assisted in establishing a diagnosis of mumps in the early development of two doubtful cases. Thus, the test has both a positive and negative value. No explanation can be offered for the two normal levels which occurred in individuals past the third decade of life. Therefore, a normal level can be found in exceptional instances of epidemic parotitis, perhaps important in older age groups. It also seems reasonable to assume that normal levels are the rule rather than the exception in extra parotid salivary mumps and in cases which are admitted for extension and complications such as orchitis, meningo-encephalitis, etc., after the parotid disease has subsided. Particularly during epidemics the diastase level may assist in establishing or excluding the diagnosis of mumps in an observation case. Cellulitis of the face, infection of the teeth and gums, pre-auricular and cervical lymphadenopathy are among the conditions which may at times create confusion.

When one is reasonably sure that pancreatitis is not present, an elevated level always points to parotitis; and conversely in a patient with gastrointestinal symptoms the diagnosis of pancreatitis can be offered in the absence of parotid involvement. The clinical picture will usually allow differentiation without difficulty. The complication of pancreatitis in mumps is not a rarity. The clinical manifestations of the syndrome are highly suggestive, but an increase in serum amylase over a recent level taken during epidemic parotitis offers confirmatory evidence.

Primary extrasalivary mumps has been reported in the literature. Primary encephalitis,<sup>29</sup> pancreatitis,<sup>30</sup> meningitis,<sup>31</sup> orchitis<sup>32</sup> have been observed. Neurological complications as myelitis<sup>33</sup> and polyneuritis<sup>34</sup> also have been noted in print. Often the evidence for the etiology is not firm. Some of these cases may have a mild parotitis and an elevated level can then be confirmatory. Others may develop parotitis following the initial extrasalivary lesion and in these cases this adjuvant diagnostic procedure can be convincing. Thus, there are innumerable ramifications for the judicious employment and clinical correlation of the test.

#### SUMMARY AND CONCLUSION

1. A brief review of the literature on serum amylase in mumps and a basis for this elevated finding were submitted.
2. A study and an analysis of a control group of 65 cases and of a series of 60 patients admitted with the diagnosis of mumps were made.
3. Elevated amylase levels were found in the great majority (95 per cent) of cases of epidemic parotitis during the active phase. This observation is not only of academic interest but can definitely be helpful in a selected group, which has been discussed.
4. In exceptional instances results may be capricious and the clinical pattern must then be relied upon.
5. Awareness by the general medical profession of the value of the serum amylase test in mumps and its limitations is desirable.



Grateful acknowledgment is due to Colonel Dooling, M.C., Chief of the Medical Service, for his guidance and encouragement; to James E. Jacobs, B.S., Chemist; and to the personnel of the chemistry department, Gorgas Hospital, Ancon, Canal Zone, for their splendid coöperation.

Gratitude is also expressed to Estelle Hall, medical secretary, for her aid in the compilation and organization of data.

### BIBLIOGRAPHY

1. LEWISON, EDWARD F.: Clinical value of the serum amylase test, *Surg., Gynec., and Obst.*, 1941, lxxii, 208.
2. ELMAN, R.: Surgical aspects of acute pancreatitis, with special reference to its frequency as revealed by serum amylase test, *Jr. Am. Med. Assoc.*, 1942, cxviii, 1265-1268.
3. POPPER, H. L., and PLOTKE, F.: Pancreatitis, disappearance of experimentally increased blood amylase and lipase, *Surgery*, 1941, ix, 706-711.
4. COMFORT, M. W., and OSTERBERG, A. E.: Serum amylase and serum lipase in diagnosis of disease of pancreas, *Med. Clin. N. Am.*, 1940, xxiv, 1137.
5. MCCORKLE, H., and GOLDMAN, L.: Clinical significance of serum amylase test in diagnosis of acute pancreatitis, *Surg., Gynec., and Obst.*, 1942, lxxiv, 439-445.
6. VORONINA, E. V.: Blood amylase in rabies as an aid in early diagnosis, *Gaz. Clin.*, 1937, xxxv, 246.
7. BARLETT, W., JR.: Amylase, effects of variations in thyroid activity, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 843-848.
8. NORBY, G.: Amylase, concentration of serum in diabetics, *Acta med. Scandinav., supp.* 1936, lxxviii, 933-935.
9. STOLFI, G.: Glycemia and serum amylase in traumatic shock and in burns, *Arch. di. sc. biol.*, 1936, xxii, 583-594.
10. DROPKIN, V. S.: Blood amylase in various diseases of brain, *Tradi Absht. nevropat. i psikrat. saratov. Univ.*, 1927, i, 89-98.
11. CASANO, C.: Amylase activity and glycemia curve in normal subjects and those with liver disturbances, *Rassegna di Terap. e pat. clin.*, 1930, ii, 235-335.
12. MAGARAN, M. E.: Blood amylase in bacterial infection, *J. eksper. biol. i med.*, 1929, xi, 142-146.
13. SUGIYAMA, N.: Esterase and amylase content of serum before and after parturition, *Sei-I-Kai Med. Jr.*, 1936, iv, 12.
14. SUGIYAMA, N.: Serum amylase of tuberculosis patients, *Sei-I-Kai Med. Jr.*, 1936, iv, 10-11.
15. CHRISTIANSEN, H.: Serum amylase in chronic alcoholics, *Hospitaltid.*, 1936, lxxiv, 79-83.
16. BODANSKY, M., and BODANSKY, O.: *Biochemistry of disease*, 1942, Macmillan Co., N. Y., p. 277.
17. BRANISTÉANU, D., and BOUTROUX, A.: Contribution à l'étude de l'élimination de l'amylase urinaire dans divers cas normaux et pathologiques, *Arch. d. mal. de l'app. digest.*, 1933, xxiii, 746.
18. DUNLOP, G. A.: Diastatic index in acute parotitis, *Lancet*, 1933, ii, 183-184.
19. HERSHHORN, S., POPPER, H. L., and SELINGER, A.: Value of determining blood diastase and blood sugar curves in pancreatitis and parotitis, *Klin. Wchnschr.*, 1931, x, 493-495.
20. BERNARD, CLAUDE: Du suc pancréatique et de son rôle dans les phénomènes de la digestion, *Arch. gén. de méd.*, 1849, xix, 60-81.
21. FOSTER, M., JR.: Notes on amylolytic ferments, *Jr. Anat. and Physiol.*, 1866-1867, i, 107-113.
22. WOHLGEMUTH, J.: Ueber eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments, *Biochem. Ztschr.*, 1908, ix, 1.
23. DAVISON, W. C.: A viscometric method for the quantitative determination of amylase, *Bull. Johns Hopkins Hosp.*, 1925, xxxvii, 281.

24. ELMAN, R., ARNESON, N., and GRAHAM, E. A.: Value of amylase estimations in diagnosis of pancreatic disease; clinical study, *Arch. Surg.*, 1929, xix, 943-967.
25. MUHLFELD, M.: Experiments on blood amylase; Columbia Univ. Dissert., 1928.
26. (a) SOMOGYI, M.: Micromethods for the estimation of diastase, *Jr. Biol. Chem.*, 1938, cxcv, 399-414.  
(b) SOMOGYI, M.: Diastatic activity of human blood, *Arch. Int. Med.*, 1941, lxxvii, 665-679.
27. HEIFETZ, C. J., PROBSTEN, J. G., and GRAY, S. H.: Clinical studies on blood diastase, *Arch. Int. Med.*, 1941, lxxvii, 824.
28. GRADWOHL, R. B. H.: Clinical laboratory methods and diagnosis, Second Edition, 1938, C. V. Mosby Co., St. Louis, pp. 233-234.
29. (a) LASSALE and PASSA: Primary mumps encephalitis, etc., *Soc. de med. mil. franc. Bull. mens.*, 1935, xxix, 97-102.  
(b) LEMIERRE ET AL.: Encephalitis without meningitis; case due to mumps, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1934, I, 109-113.
30. VELASCO, R.: Primary pancreatitis; case (mumps), *Bol. y. trab. Acad. Argent. de cir.*, 1941, xxv, 738-742.
31. (a) BERNHEIM, M., and JEANTET, R.: Primary parotitic meningitis, *Lyon méd.*, 1934, cliv, 675-677.  
(b) LITVIN, M. B.: Primary meningo-encephalitis followed by parotitis, *Sóvet. vrach. gaz.*, 1934, 1242-1245.  
(c) DALTO, A.: Primary mumps meningitis, *Semana méd.*, 1932, ii, 247-249.  
(d) DARRE', H.: Primary meningitis and meningo-encephalitis, *Rev. ont. de path. et de therap.*, 1930, i, 623-634.
32. RABINOWITZ, M. A., and SELIGMAN, B.: Primary mumps orchitis, etc., *Med. Jr. and Rec.*, 1929, cxxx, 215-216.
33. KOUSMINE, C.: Myelitis following mumps; case, *Schweiz. med. Wchnschr.*, 1934, lxiv, 235-237.
34. COLLENS, W. S., and RABINOWITZ, M. A.: Mumps polyneuritis, *Arch. Int. Med.*, 1928, xli, 61-65.

# RHEUMATIC FEVER: DIET AS A PREDISPOSING FACTOR \*

By DON CARLOS PEETE, *Kansas City, Missouri*

ALTHOUGH many careful studies have been made of rheumatic heart disease throughout the world, many misconceptions of the etiologic factors of the disease still exist. If one studies the reports from India,<sup>1, 2, 3</sup> Australia,<sup>4, 5, 6, 7</sup> Costa Rica,<sup>8</sup> Mexico,<sup>9</sup> Argentina,<sup>10</sup> Hawaii,<sup>11</sup> Iceland,<sup>12</sup> Greenland,<sup>13</sup> England,<sup>14, 15, 16, 17</sup> and the vital statistics of the United States,<sup>18</sup> he is quickly convinced that climate is but a secondary factor. Focal infection has been a greatly overemphasized factor. Careful studies have shown that many patients had their first attack of rheumatic fever after the tonsils were removed and many patients continue to have recurrence after tonsillectomy.<sup>33, 46</sup> It is generally agreed that it is good practice to remove infected tonsils in order to improve the general resistance of the individual to respiratory disease. The recent emphasis placed upon heredity by Wilson,<sup>19</sup> Reed et al.,<sup>20, 21</sup> and Irvine-Jones,<sup>22</sup> does not explain the high incidence among the poor nor the gradual decrease in the death rate in the last 30-year period in the United States, England and Australia. Glover,<sup>14</sup> in 1930, suggests that this incidence is 30 times greater among the poor than among the well-to-do. The studies of others would seem to confirm this statement. Juster's<sup>23</sup> recent studies indicate that upper respiratory infections complicate preëxisting rheumatic infections rather than initiate them. If this is a fact, the rôle of the hemolytic streptococcus organism in the etiology of the disease is questioned. It may activate the rheumatic state in a manner similar to that in which respiratory infections activate tuberculosis.

Rinehart,<sup>24</sup> in 1934, suggested that vitamin C deficiency predisposed the individual to a hemolytic streptococcus that caused rheumatic fever. Although his work has not been duplicated or confirmed in clinical experience by other investigators, we were then of the belief that there was a dietary factor that played an important part. For several years patients with rheumatic disease have been studied from the point of view of deficiencies in vitamin D, calcium and phosphorus. For a period of four years now, patients seen in both clinic and private practice, showing any signs of rheumatic fever or rheumatic heart disease, have been instructed to take daily sun baths when possible and to include one quart of milk, one egg, and cod liver oil in the daily diet. These patients were, generally, above eight years of age. There was such a marked lowering of the incidence of recurrence of the disease that it was decided to make a survey of the dietary habits of similar patients before correcting their diets. It is our belief that one's dietary habits become more or less fixed early in life and that many of the con-

\* Received for publication January 15, 1943.

From the Department of Internal Medicine, University of Kansas School of Medicine.

ceptions and prejudices toward food are acquired and kept throughout life until old ideas are replaced by new ones. We have found, also, that many people really do not know of what their diet consists since their eating has become so automatic.

Chart 1 is the list that is given to our patients with the instructions to check, after each meal, the foods eaten and to write in any not listed. We met with better coöperation when the importance of this record was impressed upon the patient. When this method is used, the deficiency in the diet is immediately revealed. The patient is then asked to keep a record, after his diet has been corrected, until his habits have been definitely altered.

Chart 2 shows the result of such a survey of 50 patients, some in the acute and some in the chronic rheumatic state, as compared with 25 normal school children in a middle-class public school. This chart is a comparison of the number of times per month the average patient with rheumatic infection takes the food indicated as compared with the average school child's diet.

A study of this table shows that the average diet of the rheumatic patient is very low in those foods that supply vitamins A and D, and the minerals, especially calcium, phosphorus and iron. There is also some deficiency in proteins and an excess in starchy foods and in the refined sugars. Both diets show a restricted use of eggs (this may have been due to the extremely high cost of eggs at the time this survey was made).

It was found, also, that many families were eating butter substitutes which have a lower vitamin and mineral ratio than butter. The economic influence is seen in the consumption of bacon: being expensive, it was treated almost as a luxury by the normal group, while a greater amount was available to the low income rheumatic group through relief measures, since it is a meat that does not require the same amount of refrigeration as fresh meat.

These findings, in some respects, are very similar to the results of the studies of Warner, Winterton and Clark<sup>31</sup> in 1935. The striking similarity is especially noteworthy in view of the fact that the work of these men did not come to my attention until after I had completed my own series of studies.

#### DIRECTIONS FOR THE USE OF THE DIET SURVEY CHART

After each meal make a single straight mark like "/", in the column opposite the different foods eaten, on the correct day of the week. Use one mark to indicate one serving. If you ate foods which are not on the chart, write them into the blank lines provided on the edge of the chart.

Example:

	Monday	Tuesday
Bread	////	///
Beef	/	
Potatoes	//	//

This would indicate that on Monday you had four slices of bread, one serving of beef, and two servings of potatoes during the day. On Tuesday, you had only three slices of bread, no beef, and two servings of potatoes.

CHART 1.

It is significant that the average number in the families of 75 rheumatic patients was 7.5 members per family, whereas the average family group in the middle class runs 4.5 members per family. It is obvious that the family with twice as many to feed on the same amount of income must of necessity buy the cheaper foods which all too often are the starchy foods. However, this survey has shown that the economic state is not the sole problem, for we have some people with an adequate income who are living on the impoverished diet. The problem in this instance is one of education and of change in the individual's dietary habits.

Those people who take full advantage of the sunshine and whose diet is rich in minerals, with a proper calcium-phosphorus ratio, or those who substitute for the sunshine a liberal amount of the fats that are rich in natural

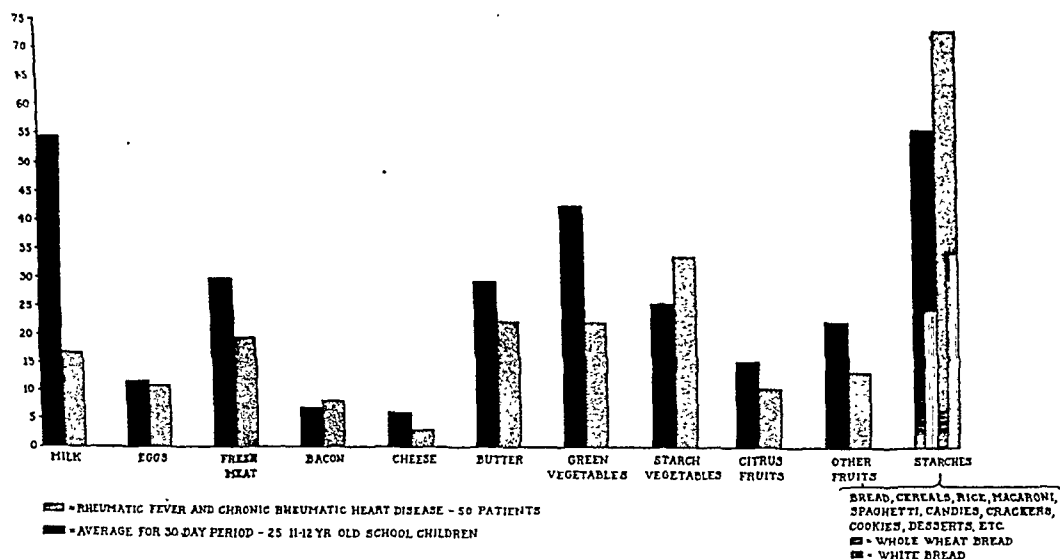


CHART 2. These figures indicate the average times per month that a group of 50 patients with acute rheumatic fever and rheumatic heart disease ate the above foods. They are compared with 25 average, normal school children.

sources of vitamins A and D have a low incidence of rheumatic fever and its sequelae. This fact is emphasized by the rarity of rickets and dental caries among the primitive Eskimo tribes who live upon a high protein diet made up largely of fish and oils. The mothers nurse their babies until the teeth erupt because the child must be able to chew the meat which is a large part of his very earliest diet. Those tribes which have changed their habits of eating to include flour, sugar and other starches show severe rickets, scurvy, and dental caries and rheumatic disease.<sup>12, 18, 25</sup> It is of particular significance that Harrington,<sup>26</sup> in his experience in Charleston, South Carolina, found a very low incidence of rheumatic infection among those people whose occupation was primarily fishing, and conversely, a high incidence among the workers in the industrial and rural districts. The experience of John Schmidt,<sup>47</sup> as a medical missionary in several colonies in Paraguay, South

America, is noteworthy. During a 15 months' stay he examined 1300 people and found only three with rheumatic fever, two boys five and eight years of age and a girl 14. These people have an abundance of milk, eggs, butter, cheese and meat. Lettuce, green beans and potatoes are plentiful but other vegetables are scarce as is wheat flour.

The findings of Heinbecker and Irvine-Jones,<sup>27</sup> following their immunologic studies among the Eskimos, substantiate the theory that dietary factors influence immunologic reactions. Their work shows that after the age of 12 the Eskimos, living as a primitive people far away from scarlet fever, diphtheria and rheumatic fever, are immune to scarlet fever and diphtheria and showed only mildly positive skin reactions, in a small number of cases, to filtrates from rheumatic fever.

In 1938 Stott<sup>1</sup> published convincing evidence to show that in a tropical climate rheumatic fever and rheumatic heart disease are fairly common, averaging about six cases of acute rheumatic infection for every 1,000 admissions to the hospitals of India. It is also interesting to note that the highest admission rate occurred during the cold, dry months and not during the hot, damp, monsoon months. Mitra,<sup>28</sup> in the same medical journal, published evidence to show that many of these Indian communities live on diets low in calcium, phosphorus and proteins; some are not only vegetarians, but it was also found that they did not compensate for the lack of meat by drinking milk or eating eggs. Fernando<sup>29</sup> reports from the hospitals of Ceylon that an incidence of 2.2 per cent of the total admissions is due to rheumatic infection. These figures compare closely with those figures of the five general hospitals in Victoria, Australia. Nicholls,<sup>30</sup> in 1936, showed that malnutrition is widespread among the lower classes and that their diets are deficient both in quality and quantity when compared with the upper classes.

A study of rheumatic fever among the Aborigines in Australia and among the Indian tribes in the United States<sup>32</sup> reveals that the disease occurs among these the same as it does in other races in the same climate. Studies in Australia and in England point out that although the incidence of rheumatic fever is much higher among the poorer class, it is the middle-class poor, rather than the very poor who are on relief, who suffer most. This would suggest that those on relief are living on better diets since they may not choose the "tasty" foods but must accept that which is given to them. These studies in Australia refute the common belief that dampness is an important etiologic factor. Hedley's<sup>33</sup> surveys also indicate that the disease is one of poverty rather than one of climate. Paul,<sup>34</sup> at New Haven, Connecticut, and Coombs,<sup>35</sup> in Bristol, England, found that the amount of rheumatic fever was lowest in private schools, higher in the rural schools and highest in the city public schools. These findings indicate that there must be something in the individual's living habits that will protect him or predispose him to the infection. Whereas reports from Mexico,<sup>9</sup> England,<sup>14, 15, 16, 17</sup> Holland,<sup>36</sup> Costa Rica,<sup>8</sup> Hawaii,<sup>11</sup> India,<sup>1, 2, 3</sup> Australia,<sup>4, 5, 6, 7</sup> Argentina,<sup>10</sup> and from

various states in the United States<sup>18</sup> indicate that rheumatic fever and rheumatic heart disease are found in nearly every country in the world except among the native, primitive Eskimos, the incidence of the disease usually is seen to vary with the climatic conditions.

During the 30 year period, 1910 to 1940, there was a general downward trend in the death rate due to rheumatic fever in the United States as shown

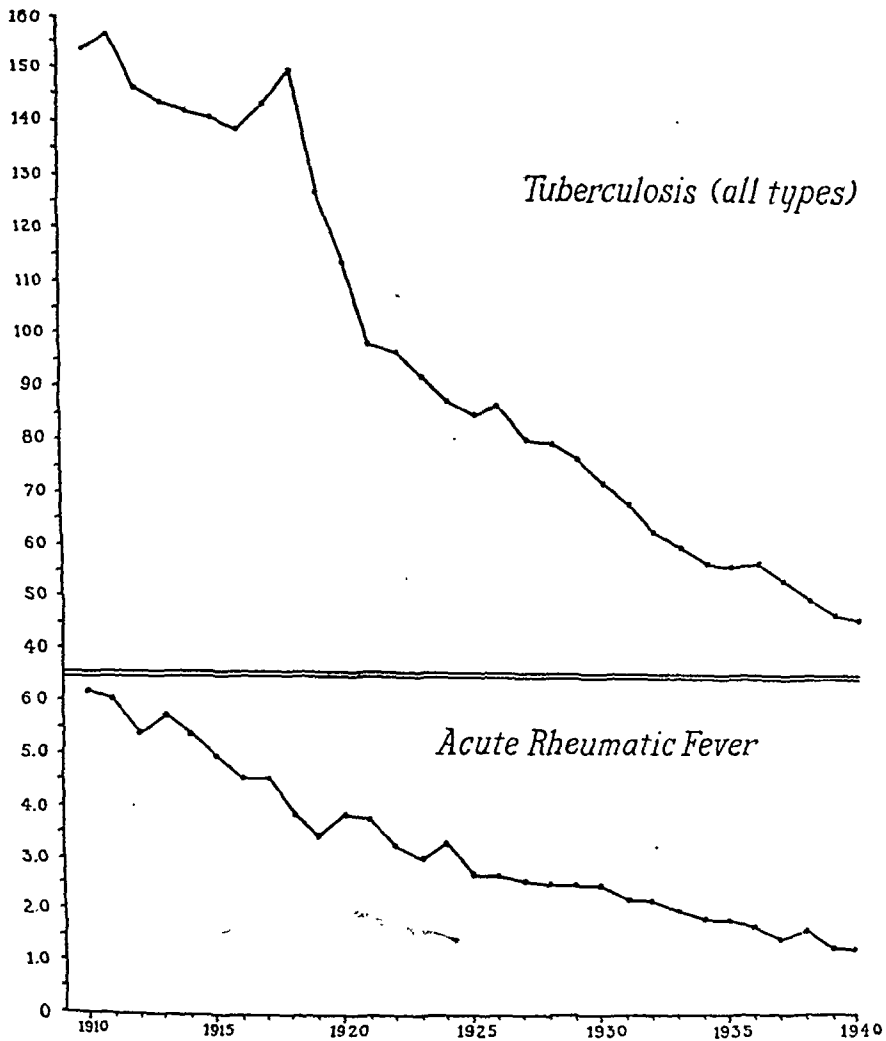


CHART 3. Graph, comparing rheumatic fever and tuberculosis, shows a decline of death rates per 100,000 population.

in the graph. This decrease in death rate has been noted in Australia and England also. A similar trend is shown in the graph relating to tuberculosis. It is believed that this reduction is the result of three very important factors which will require continued emphasis if this improvement is to progress. First, there must be adequate food available at a price the masses can afford; second, people must be educated to the importance of an adequate diet, and



the value of sun bathing; third, the necessity for early medical care with complete bed rest until all signs of activity have subsided.

In table 1, which is taken from the Vital Statistics of the Department of Commerce—Special Reports, 1940—is shown the death rate due to acute rheumatic fever and chronic rheumatic heart disease during 1940 for each 100,000 population and also the actual number of deaths for each state. The death rate for pellagra is also shown. In order to indicate the amount of dairy products available throughout the United States, an attempt was made to determine the number of cows per population. No statistics were available to demonstrate this important fact; it was possible, however, to show the percentage of farms without cows and pigs, so this information was included in table 1, in order to demonstrate, generally, the relation between the food available and the incidence of rheumatic disease and pellagra, which is known to be a deficiency disease.\* The death rate for pellagra would indicate that the problem of adequate diet is far from solved in our own country. In studying these figures one sees that many of our southern states have a higher incidence of rheumatic diseases than some of the more northern states. The answer to this is found, we believe, in the type of crops that are raised in the different sections of the country. In the South, where cotton is king, or in the industrial centers where the crop or labor is exchanged for money, the individual in turn buys those foods which are the most pleasing and which are the cheapest; usually these foods are the starchy ones, with meat in deficient amounts. In table 1 the percentage of farms without cows and hogs in the United States is shown and one sees that there is some relation between the food available and the incidence of rheumatic infection.

It is interesting to note that there was a great acceleration in the downward trend of the death rate from both rheumatic fever and tuberculosis after the discovery of the true cause of rickets by Findlay,<sup>37</sup> in 1908, and following Mellanby's<sup>38</sup> experiments on rickets in 1918. It is possible that the preventive measures taken to lower the incidence of rickets, in addition to the public health measures instituted to control tuberculosis, have been responsible for much of this lowering of the death rate from rheumatic fever. To show better many common features of rheumatic fever and rickets I wish to quote from an excellent review by Park<sup>39</sup> upon the etiology of rickets in 1923: "*The Occurrence of Rickets*. It is a disease found in cities. It is most prevalent in those nations whose wealth and industrial development have brought about most fully the substitution of artificial conditions of living in place of the simple conditions which nature intended. Wherever civilization of this artificial character establishes new contacts, rickets begins to appear. The disease has appeared in India where the designs of nature have been interfered with by religious customs to be mentioned later. The disease never occurs among peoples living under natural conditions. Savages may starve and may become the victims of pestilence, but they do not develop

\* We do not believe that vitamin B deficiency is a predisposing factor to rheumatic fever.

TABLE I  
Statistics

States	Vital Statistics			Percentage of Farms without cows and hogs		Death Rates (no. per 100,000 enumerated population)	
	Deaths from selected causes in the United States (1940) Dept. of Commerce Reports			Bureau of Agricultural Economics			
	Acute Rheumatic Fever	Chronic Rheumatic Disease of the Heart	Pellagra (except alcoholics)	% Farms without milch cows	% Farms without hogs and pigs (1939)	Acute Rheumatic Fever	Chronic Rheumatic Disease of the Heart
New England:							
Maine	11	212	—	28.6	72.5	1.3	25.0
New Hampshire	5	129	—	34.6	82.4	1.0	26.2
Vermont	2	110	—	18.9	78.5	0.6	30.6
Massachusetts	30	1,142	6	49.4	89.5	0.7	26.5
Rhode Island	3	156	1	39.6	88.0	0.4	21.9
Connecticut	24	337	3	38.9	91.0	1.4	19.7
Middle Atlantic:							
New York	177	3,478	18	24.4	72.9	1.3	25.8
New Jersey	77	913	9	51.2	79.1	1.9	21.9
Pennsylvania	172	2,263	17	25.8	51.1	1.7	22.9
East North Central:							
Ohio	98	1,612	9	20.0	38.2	1.4	23.3
Indiana	39	780	10	16.8	27.3	1.1	22.8
Illinois	96	1,791	20	13.7	24.1	1.2	22.7
Michigan	45	1,058	10	22.4	52.7	0.9	20.1
Wisconsin	53	589	3	10.4	41.1	1.7	18.8
West North Central:							
Minnesota	41	569	5	12.2	31.8	1.5	20.4
Iowa	27	600	3	10.0	14.9	1.1	23.6
Missouri	39	1,157	13	15.8	23.8	1.0	30.6
North Dakota	14	79	2	16.4	38.6	2.2	12.3
South Dakota	11	87	1	16.7	31.3	1.7	13.5
Nebraska	9	268	2	13.7	31.7	0.7	20.4
Kansas	9	393	6	17.3	46.5	0.5	21.8
South Atlantic:							
Delaware	5	70	—	38.1	46.2	1.9	26.3
Maryland	35	473	7	34.5	45.3	1.9	26.0
Dist. of Columbia	10	133	1	—	—	1.5	20.1
Virginia	49	543	59	24.2	34.1	1.8	20.3
West Virginia	24	274	11	19.6	41.6	1.3	14.4
North Carolina	68	522	169	35.3	31.1	1.9	14.6
South Carolina	42	314	161	36.2	24.2	2.2	16.5
Georgia	46	381	251	26.6	23.7	1.5	12.2
Florida	30	360	72	56.7	48.4	1.6	19.0
East South Central:							
Kentucky	41	515	60	19.0	35.3	1.4	18.1
Tennessee	70	628	102	21.2	29.7	2.4	21.5
Alabama	48	526	244	21.6	25.7	1.7	18.6
Mississippi	32	476	169	34.1	27.3	1.5	21.8
West South Central:							
Arkansas	24	237	104	25.8	31.4	1.2	12.2
Louisiana	20	450	75	30.9	27.3	0.8	19.0
Oklahoma	25	330	61	14.6	35.2	1.1	14.1
Texas	68	634	354	19.1	39.6	1.1	9.9
Mountain:							
Montana	5	121	1	29.5	60.8	0.9	21.6
Idaho	9	99	3	18.3	42.5	1.7	18.9
Wyoming	3	40	—	21.0	56.0	1.2	16.0
Colorado	11	257	1	26.5	52.4	1.0	22.9
New Mexico	8	67	19	46.6	61.6	1.5	12.6
Arizona	5	55	5	62.8	86.0	1.0	11.0
Utah	10	153	3	22.2	47.3	1.8	27.8
Nevada	—	22	1	34.1	60.1	0	20.0
Pacific:							
Washington	12	410	5	29.1	70.3	0.7	23.6
Oregon	11	280	4	24.6	63.4	1.0	25.7
California	32	1,337	43	61.0	84.9	0.5	19.4

rickets. The disease does not occur in the native parts of Africa and is exceedingly rare in China and Japan. It occurs rarely in the tropics, and is rare in the Arctic regions. . . . The seasonal variation in rickets was beautifully demonstrated in the pathological studies of Schmorl. These studies showed that rickets may begin at any time, but the highest percentage of early manifestations of the disease is between November and May. The percentage of cases with signs of healing increased as the summer progressed and reached its highest point in the autumn, only to fall again as the winter months came." The many different theories that were advanced concerning the cause of rickets were not unlike the many theories discussed as the cause of rheumatic fever.

For some time we have been impressed with the more severe form of rheumatic fever among the Negro and Mexican children. This fact has been recognized by Hedley,<sup>33</sup> and Ash.<sup>40</sup> Boas<sup>41</sup> has pointed out the severity of rheumatic carditis in the adult Puerto Rican immigrants in New York City. We have explained this difference in severity and incidence among those people with dark skins as being the result of their inability to take advantage of the reduced amount of actinic rays in a more northern climate than that to which they are accustomed. This difference was noted among those having rickets. Park<sup>39</sup> states: "A study was made by Hess and Unger of the diets of the negro mother in a negro district of New York City where rickets was exceedingly prevalent among breast-fed children. The negroes were, for the most part, immigrants from the West Indies where they lived chiefly on meat or fish, rice and potatoes, tea, coffee and cereal. Milk was taken in small quantity and fruit rarely. The vegetables, which were taken in small amounts, were usually canned. In New York City the women lived indoor lives. The striking points brought out in the study were that the mothers had exchanged an outdoor life in the tropics for an indoor life in the temperate zone and a dietary in which green vegetables and green leaves figured largely for one in which those articles of food were almost entirely lacking."

This similarity between rheumatic fever and rickets is manifested not only in the incidence socially and by geographic distribution, but there is also a close relation between the tissues involved in the two diseases. Rheumatic fever involves primarily the mesodermal or the connective tissue structures of the body, whereas rickets is a disease involving the cartilage and the bone, which is, of course, derived from the connective tissue. Both of these diseases usually have a secondary anemia and the individuals are generally underweight. These facts certainly suggest the possibility that a deficiency in vitamin D from a lack of sunshine, when not compensated by vitamin D in the diet, and associated with diets too low in calcium and phosphorus, effects a change in the immune forces of the individual. It is not at all unlikely that vitamin D is very essential in the normal development of all mesodermal structures. We know that it is stored in the fat cells, which are a modified form of connective tissue cell, and we know also that it is found

most often stored in the liver. Cannon,<sup>42</sup> in a recent discussion of antibodies and the protein reserves, states that: "Antibodies are substances which, after intracellular formation, are excreted or secreted into the blood or lymph. The accumulated evidence of 50 years leaves little doubt but that the macrophage (broadly defined) is the principal cell concerned with their production. This does not exclude the possibility, however, that other types of cells may also participate to some extent either in synthesis of antibodies or in the development of the antibody mechanism." In his paper Cannon clearly emphasizes the importance of protein in antibody production.

Another fact to be noted about the macrophage system, which has become known as the reticuloendothelial system, is that it is made up of cells that have the ability to take up particulate matter and to store foreign substances brought to them in colloidal solution.<sup>43</sup> The macrophage system or the reticuloendothelial system is derived from mesodermal tissue, the same tissue from which bone and connective tissue are derived. These facts also lead me to believe that vitamin D may be necessary in the normal development of all mesodermal structures. If this theory is true, it could account for the infection being so much more common in childhood during the developmental period. This could be the answer to the statement made by Coburn<sup>44</sup> in 1932: "The collected observations on the relation of the activity of the rheumatic process to hemolytic streptococcus, and the failure to detect a single serological type of organism associated only with rheumatic fever, have led to the conception that the specificity of the rheumatic response, like the reaction in certain other streptococcus diseases, depends not entirely upon the character of the parasite but is perhaps related to some individual mechanism of the rheumatic subject." This theory could explain also the reason for the statement of Swift,<sup>45</sup> in 1940: "... crowding, poor housing and poor nutrition seem to play almost as important unfavorable rôles in hot as in cold climates."

A most recent study of the epidemiology of juvenile rheumatism in the British Isles, by Morris and Titmuss,<sup>17</sup> led to these conclusions: "Mortality on the whole increases with the density of population; this seems to be a function of the greater poverty in towns. The depressed rural districts return rates as high as the worst of the big towns. No evidence was found to suggest that the artisan stratum is particularly prone to the disease. Climate seems of little importance. Correlation with overcrowding was inconclusive. The facts elucidated strengthen the view that the whole complex of poverty is involved in the production of juvenile rheumatism."

Because of these facts, patients have been studied recently with a consideration of signs of previous disturbances in the mineral metabolism, i.e., dental caries, scoliosis, flaring of the ribs, or thoracic deformities known to be acquired, bow legs and knock knees. This study has been very interesting, for we find many of our patients show at least one of these signs, and some show evidence of several such disturbances. This fact, coupled with

the result of a dietary survey showing foods inadequate in calcium, phosphorus and vitamins A and D, and too high a ratio of carbohydrates, has suggested the feasibility of treatment with high potency vitamins A and D\* and an increase in calcium and phosphorus values in the diet. Preliminary studies in a small series of patients so treated are promising and warrant continuation of the experiment on a large scale.

The following evidence indicates that diet and sunshine are the most important predisposing factors in the causation of acute rheumatic fever:

(a) The incidence of acute rheumatic fever and rheumatic heart disease increases as exposure to the sun decreases.

(b) Very low incidence of rheumatic infection exists in those countries which have an abundance of proteins and fish oils in the diet.

(c) The incidence of rheumatic infection is lowest in the private schools, next lowest in the rural schools and highest in the public schools.<sup>34, 35</sup>

(d) Poverty, and not dampness, is the predisposing factor.<sup>33, 4, 17</sup>

(e) Holland, with a cold, damp climate, shows a low incidence of rheumatic heart disease.<sup>36</sup>

(f) Those states in the United States which are primarily farm and dairy states have a lower incidence of the infection than those states which are largely industrial, or whose chief crops are cotton, tobacco and similar produce.

(g) A study of 76 patients with rheumatic heart disease and acute rheumatic fever reveals that the average size family is 7.5 persons per family. This indicates that persons in low income groups with large families have to spread the milk, butter, eggs, meat and fresh vegetables "too thin."

(h) There have been very few recurrences of active infection when families have coöperated in the correction of diets and in the addition of cod liver oil to the diet.

(i) Studies of the vital statistics, 1910 to 1940, show that the death rate for rheumatic fever follows the same tendency as that of tuberculosis, namely, a downward trend with improvement in economic conditions and education. Both of these diseases are primarily diseases of poverty.

(j) Poor dietary habits have been found to exist among those with adequate financial means. This condition was revealed by our method of dietary survey, using chart 1.

(k) Those races having much skin coloring are more susceptible to rheumatic fever when taken to climates having less sunshine than that to which they are accustomed; they also have a more virulent form of the disease.

(l) Seasonal variation is noted in the incidence of the disease, being more common in the winter and spring, following a period of inability to benefit from exposure to the sun.

\* Vitamin A 25,000 units and vitamin D 50,000 unit capsules were supplied by Brewer and Company.

(m) Those people who live in high altitudes, because of cold climate and a consequent lack of body exposure to the sun, have a higher incidence of rheumatic infection when they do not compensate for these deficiencies by increased quantities of vitamin D.

(n) Immunologic studies among the Eskimos show that there is a natural immunity after the age of 12 to scarlet fever, diphtheria and also to filtrates from rheumatic fever patients.<sup>27</sup>

Finally, it is my belief that this deficiency, which closely follows the incidence of clinical rickets, alters the individual's immunity to the infective organism that produces the clinical picture of acute rheumatic fever. The importance of adequate amounts of vitamins A and D, milk, protein and the value of sun bathing cannot be overemphasized in the prevention of this crippling disease and its recurrences.

I am indebted to Drs. Wahl, Major, Clendening and Hashinger for their criticisms and advice in the preparation of this paper.

#### BIBLIOGRAPHY

1. STOTT, H.: Frequency of rheumatic infection in India, *Indian Med. Gaz. (Calcutta)*, 1938, lxxiii, 330.
2. KUTUMBIAH, P.: Rheumatism in childhood and adolescence, *Indian Jr. Pediat.*, 1941, viii, 65.
3. BASU, U. P.: Rheumatic heart disease, *Indian Med. Gaz. (Calcutta)*, 1941, lxxvi, 11.
4. MADDOX, KEMPSON: Metropolitan and rural incidence and distribution of acute rheumatism and acute rheumatic heart disease in New South Wales, *Med. Jr. Australia*, 1937, i, 394.
5. Report on epidemiology of rheumatic infection in South Australia, *Med. Jr. Australia*, 1940, i, 461.
6. GRAHAM, H. BOYD: The incidence of rheumatic infections in Victoria, *Med. Jr. Australia*, 1937, i, 944.
7. JONES, E. BRITTEN: The rheumatic child, *Med. Jr. Australia*, 1934, ii, 273.
8. CARRILLO, E. GARCIA: San Jose, Costa Rica. Rheumatic carditis in a tropical country, *Am. Heart Jr.*, 1942, xxiii, 170-174.
9. CHAVEZ, IGNACIO: Mexico City: The incidence of heart disease in Mexico, *Am. Heart Jr.*, 1942, xxiv, 88.
10. COSSIO, PEDRO: Heart disease in the Argentine, Lewis A. Connor Lecture before the American Heart Association, June, 1942.
11. DOOLITTLE, S. E., and TILDEN, I. L.: Rheumatic heart disease in Hawaii, *Hawaii Med. Jr.*, 1941, i, 7-11.
12. THOMAS, WILLIAM A.: Health of a carnivorous race, *Jr. Am. Med. Assoc.*, 1927, lxxxviii, 1559.
13. DUFFIELD, WARREN L.: Greenland health conditions, *New York State Jr. Med.*, 1934, xxxiv, 403.
14. GLOVER, J. ALLISON: Incidence of rheumatic diseases (Milroy Lecture), *Lancet*, 1930, i, 499.
15. GLOVER, A.: Discussion on the etiology of acute rheumatism and chorea in relation to social and environmental factors, *Proc. Roy. Soc. Med.*, 1934, xxvii, 953.
16. CAMPBELL, N., and WARNER, E. C.: A study of rheumatic disease in children, *Lancet*, 1930, i, 61-66.

17. MORRIS, J. N., and TITMUSS, R. N.: Epidemiology of juvenile rheumatism, *Lancet*, 1942, ii, 59-63.
18. Special Reports—Vital Statistics for 1940—The United States Department of Commerce. Vol. 15, No. 7, p. 69.
19. WILSON, M. G.: Rheumatic fever: Studies of the epidemiology, manifestations, diagnosis and treatment of the disease during the first three decades, 1940. Commonwealth fund. London.
20. REED, F. M., CIOCCO, A., and TAUSSIG, H. P.: Frequency of rheumatic manifestations among relatives, *Am. Jr. Hyg.*, 1938, xxvii, 719.
21. GOULD, R. L., CIOCCO, A., and REED, F.: Rheumatic infection in families of patients, *Jr. Clin. Invest.*, 1938, xviii, 213.
22. IRVINE-JONES, EDITH: Acute rheumatism as a familial disease, *Am. Jr. Dis. Child.*, 1934, xlv, 1184.
23. JUSTER, IRVING R.: The relationship of upper respiratory infection to rheumatic activity in chronic rheumatic heart disease, *ANN. INT. MED.*, 1942, xvi, 1137.
24. RINEHART, J. F., and METTIER, S. R.: The heart valves and muscles in experimental scurvy with superimposed infection: with notes on the similarity of the lesions to those of rheumatic fever, *Am. Jr. Path.*, 1934, x, 61.
25. URQUHART, J. A.: The most northerly practice in Canada, *Canad. Med. Assoc. Jr.*, 1933, xxxiii, 193.
26. HARRINGTON, PAUL: Personal Communication, 77th Evacuation Unit, U. S. Army.
27. HEINBECKER, PETER, and IRVINE-JONES, EDITH: Susceptibility of Eskimos to the common cold and a study of their natural immunity to diphtheria, scarlet fever and bacterial filtrates, *Jr. Immunol.*, 1928, xv, 395.
28. MITRA, DURGA DAS: Dietary habits of some communities, *Indian Med. Gaz.*, 1938, lxxviii, 280.
29. FERNANDO, P. B.: Rheumatic heart disease in Ceylon, *Quart. Jr. Med.*, (new series), 1939, viii, 261.
30. NICHOLLS, L.: Nutritional survey of poorer classes in Ceylon, *Ceylon Jr. Sci.*, Section D, Colombo, 1936, iv, 1.
31. WARNER, E. C., and WINTERTON, F. G.: Dietetic study of cases of juvenile rheumatic disease, *Quart. Jr. Med.*, 1935, iv, 227-246.
32. PAUL, J. R., and DIXON, G. L.: Climate and rheumatic disease, a survey among American Indian school children in northern and southern localities, *Jr. Am. Med. Assoc.*, 1937, cviii, 2096.
33. HEDLEY, O. F.: Rheumatic heart disease in Philadelphia hospitals, *Pub. Health Rep.*, 1940, Reprint No. 2195, p. 134.
34. PAUL, J. R., HARRISON, E. R., SALINGER, R., and DEFOREST, G. K.: The social incidence of rheumatic heart disease, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 301.
35. COOMBS, C. F.: The incidence of juvenile cardiac rheumatism in the West of England, *Proc. Roy. Soc. Med.*, 1930-1931, xxiv, 1611-1612.
36. VAN BREEMAN, J.: Types of rheumatic disorders most prevalent in Holland, *Med. Jr. and Rec.*, 1928, cxxviii, 489.
37. FINDLAY, L.: The etiology of rickets: a clinical and experimental study, *Brit. Med. Jr.*, 1908, ii, 13.
38. MELLANBY, E.: The part played by an 'accessory factor' in the production of experimental rickets, *Jr. Physiol.*, 1918, lii, 11.
39. PARK, EDWARDS A.: The etiology of rickets, *Physiol. Rev.*, 1923, iii, 106.
40. ASH, RACHEL: Rheumatic infection in childhood: influence of type of onset and calendar year of onset, *Am. Heart Jr.*, 1941, xxii, 439.
41. BOAS, E. P.: Rheumatic fever in adult Puerto Rican immigrants, *Am. Jr. Med. Sci.*, 1931, clxxxii, 25.
42. CANNON, PAUL: Antibodies and the protein reserves, *Jr. Immunol.*, 1942, xlv, 2.

43. MAXIMOW, A. A., and BLOOM, WM.: A textbook of histology, W. B. Saunders, Philadelphia, p. 95, 1942.
44. COBURN, A. F., and PAULI, R. H.: Studies on the relationship of *Streptococcus hemolyticus* to the rheumatic process, Jr. Exper. Med., 1932, lvi, 609.
45. SWIFT, H.: Public health aspects of rheumatic heart disease, Jr. Am. Med. Assoc., 1940, cxv, 1509.
46. ASH, RACHEL: Influence of tonsillectomy on rheumatic infection, Am. Jr. Dis. Child., 1938, lv, 63.
47. SCHMIDT, JOHN R.: Personal Communication.



# SHORT P-R INTERVAL ASSOCIATED WITH PROLONGATION OF QRS COMPLEX; A CLINICAL STUDY DEMONSTRATING INTERESTING VARIATIONS \*

By OSCAR A. PALATUCCI, MAJOR, M. C., A. U. S., and JAMES E. KNIGHTON, LT. COL., M. C., A. U. S., F.A.C.P.

BECAUSE of the recent interest in the syndrome of the short P-R interval associated with a prolonged QRS complex, without organic heart disease (Wolff-Parkinson-White syndrome), as evinced by the publication of several articles on this subject in the past two years, it is desired to add four other cases to the rapidly growing list of reports. In accordance with the sex predominance previously reported<sup>1</sup> all of these have occurred in healthy, young male subjects. Other characteristics include absence of definite organic heart disease, slurring of the initial ventricular deflection, a peculiar susceptibility to attacks of paroxysmal tachycardia, either supraventricular or ventricular in type, and reversal to normal electrocardiographic pattern either spontaneously or after exercise or after atropine administration. Use of this drug resulted in reversion to a normal type of tracing in one of our cases; there was no appreciable effect in two; and in the remaining one a "paradoxical" effect was demonstrated. Marked T-wave variations have also been seen, especially in the limb leads, both spontaneously and after atropine.

In 1937 Bishop<sup>2</sup> reviewed the literature; and two years ago Hunter, Papp and Parkinson<sup>3</sup> enumerated the various ingenious mechanisms advanced to explain this phenomenon. The most plausible and generally accepted explanation is that proposed by Wolferth and Wood,<sup>4</sup> namely ventricular asynchronism due to the premature stimulation of one ventricle through an abnormal conducting pathway. These authors, in their most recent communication,<sup>5</sup> have stated their reasons in support of such an hypothesis, and offer experimental evidence in its behalf. Our prime purpose in presenting these cases is to report our observations of the electrocardiographic changes noted, with particular reference to the variations in the terminal ventricular complex.

## CASE REPORTS

*Case 1.* On July 15, 1942, one month after his induction, F. L. G., a slightly undernourished but well developed white male adult, 24 years of age, was admitted to the Station Hospital because of dermatitis venenata. His father died at 52 years of age of an acute cardiac episode, and his mother died at the age of 40 of diabetes. Of seven siblings, five are living and well, one is said to have valvular heart disease, and one died at the age of 42 of an acute cardiac condition. His past history re-

\* Received for publication March 27, 1943.

vealed the usual infectious diseases and pneumonia as a child. No history of diphtheria, scarlet fever, or any of the rheumatic manifestations could be obtained. At 20 years of age he had a cyst (reported to be of sebaceous type) removed surgically from the anterior surface of his neck. He always felt weak and undernourished and could never do any hard work. For the past five years, after exercise, his heart would beat fast and he would "get pains around his heart" and shortness of breath. At times his heart would "run away." Even while at rest his heart would take a sudden jump, and he felt as "though the blood flowed fast through it." At times, also, he could feel his heart beating very rapidly to the left and below his left nipple.

There was no history of venereal infection or serious injury. He smoked one pack of cigarettes daily; no alcohol or drugs were used.

Physical examination revealed an apparently well male adult 6 feet 5 inches tall, weighing 124.5 pounds. There was a diffuse papular rash over both forearms and axillae, and both legs. He showed a well healed vertical scar in the midline of his neck just over the thyroid cartilage. The examination was otherwise not remarkable except for a mild tachycardia, rate 108, and a fine tremor of the outstretched hands. Blood pressure was 114 mm. Hg systolic and 70 mm. diastolic.

Laboratory data: Urinalysis was normal chemically and microscopically. Blood—red blood cells 5.35 M., hemoglobin 17.5 gm., white blood cells 7,700. Differential formula: polymorphonuclears 68, lymphocytes 27, monocytes 5. Fasting blood sugar was 131 mg. Blood cholesterol 223 and 221 mg. Basal metabolic rates were reported plus 37 and plus 36. Following medication with phenobarbital gr. one three times daily, rechecks were obtained and reported minus 8 and plus 4.

Roentgenogram of the chest revealed a heart of normal configuration and no lung disease.

Electrocardiogram (figure 1-a) on admission showed a tracing resembling left bundle branch block of the discordant type. It showed a regular rhythm with a rate of 85, a P-R interval which varied between .10 and .12 and a QRS width of .11.  $T_1$  was inverted, and in Lead IV-F there was an absent S-wave with slightly elevated RT segment. The ascending limb of  $R_1$  arose from the P-wave before the latter had returned to the base line. The initial ventricular deflection was slurred in all leads.

In order to test the effect of atropine on our first patient he was given the drug in doses of gr. 1/100 every four hours until he complained of dry mouth and blurring of vision, and showed dilated pupils. A tracing at this time showed, paradoxically, a marked respiratory arrhythmia and bradycardia (figure 1-b). The rate was slowed to slightly less than 60, the P-R interval increased to .13 and the width of the QRS was shortened to .08. These values varied somewhat in the different leads but for the sake of uniformity, Lead II was used for their determination. However, the most interesting changes occurred in the terminal ventricular complexes.  $T_1$  which had previously been inverted now became upright,  $T_3$  closely resembled the "coronary T", and  $T_{4-F}$  became much taller and slightly wider. A few minutes later a tracing was taken following exercise. The only discernible change was an increase in rate. Evidences of the arrhythmia persisted. Exercise alone, without the added effect of atropine, had previously caused  $T_1$  to become upright without any other demonstrable change. The tracing immediately following the ingestion of 300 c.c. of ice water showed only a mildly diphasic  $T_1$ . The effects of changes in posture consisted mainly in alteration of the T-wave.  $T_1$  which was inverted while in the supine position became practically isoelectric while sitting, and only slightly inverted while standing.  $T_2$  was essentially unchanged.  $T_3$ , which was upright and well marked in the supine position, became of low voltage while sitting and was barely discernible while standing.  $T_4$  was unchanged.

Case 2. W. M. M., a well nourished and developed adult colored male, 24 years

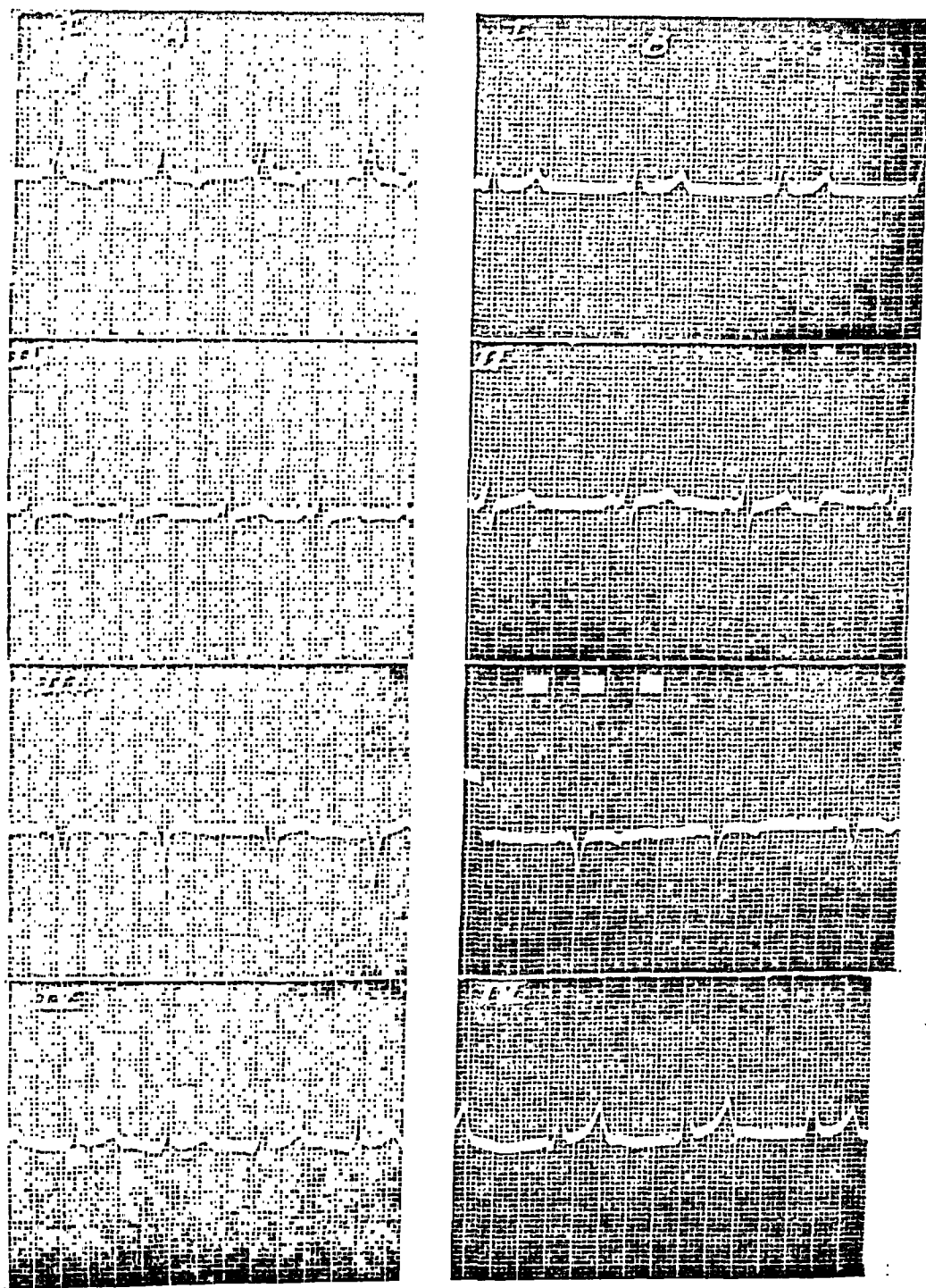


FIG. 1. *Case 1.* A—original electrocardiogram; B—after atropine. Note bradycardia, respiratory arrhythmia, and alterations of T-waves.

of age, was admitted on October 10, 1942, because of paroxysmal tachycardia. He was of normal habits with negative past and family history. For the preceding three years he had had attacks of rapid heart action about twice weekly lasting two to three minutes. During these episodes precordial pain and dyspnea were noted. On

the morning of October 10, while doing field exercises, he experienced one of his attacks, and his pulse rate at that time was about 200. This was witnessed by the dispensary medical officer. By the time he had reached the hospital the tachycardia had subsided, his pulse and heart rates being 78. Physical examination was essentially normal. There was no cardiac enlargement, nor were there any murmurs or thrills. The only positive finding was a chronic laryngitis. The Kahn reaction was negative, and urine and blood counts were within normal limits. An electrocardiogram taken on October 12, 1942 (figure 2-a) showed a tracing resembling left bundle branch block of the discordant type. There was sinus arrhythmia and bradycardia with a P-R interval of .08 to .09 second and the QRS duration was .12 to .14 second in different leads. The initial ventricular deflection was slurred in all leads, and as in the first case, arose from the P-waves before the latter had reached the base line. All T-waves were upright. This patient was also atropinized up to tolerance, but the only significant change observed (figure 2-b) was inversion of  $T_1$ , so that it simulated the coronary T-wave. The heart rate was also slightly increased.

Case 3. Sgt. W. R. J., white, age 20 years, was admitted to the hospital on December 17, 1942, with the complaints of tachycardia, dyspnea, and irregular heart action. These symptoms had been noted after exertion for a period of two years, but it was stated that, during recent months, the frequency and severity of attacks had been increasing and followed less strenuous exercise. The cardiac symptoms had usually lasted from five to 10 minutes and were sometimes associated with "blind spells," although syncope had not occurred. Precordial pain had not been noted at any time. Carotid sinus pressure had not produced cessation of tachycardia, but the patient thought that holding the breath had hastened relief.

Prior to induction the patient had been a student. He had completed two years of military service, his work being operation and maintenance of teletype apparatus. Symptoms were first noted shortly after his induction into the service.

Past medical history revealed nothing of importance, and family history showed no incidence of cardiac disease in parents or six siblings. Habits had been normal, with very moderate use of tobacco and alcohol.

The soldier was 73 inches in height, and his weight was 164 pounds. Aside from the cardiovascular system the physical examination revealed entirely normal findings, and laboratory examinations afforded nothing of interest. The heart presented no enlargement and there was no irregularity. The rate at rest was 100 per minute, increased to 136 on mild exercise, and returned to 102 after two minutes of rest. With the accelerated rate after exercise the apical first sound was accentuated, but no murmurs were heard at any time. No thrill was present. The blood pressure varied from 142 mm. Hg systolic and 96 mm. diastolic, on admission, to 108 mm. Hg systolic and 68 mm. diastolic on later determinations.

On the day after admission an electrocardiogram (figure 3-a) revealed auricular and ventricular rates of 70 per minute. The P-R interval varied from .08 to .11 second in different leads. The QRS complexes measured .12 to .14 second, with the features of left bundle branch block of the discordant type. As in the other cases, the initial ventricular deflection was slurred. The RS-T segments were slurred in all leads. The T-waves in Lead I were diphasic, but upright and peaked in Leads II and III. In Lead IV-F the T-waves were sharply inverted.

After hypodermic administration of three doses of atropine sulphate, each gr. 1/150, at intervals of four hours a second electrocardiogram was made. No appreciable change was noted. Six days later cardiograms were made before (figure 3-b) and after exercise. Both of these tracings revealed normal sinus rhythm. The P-R interval measured .16 second. QRS was diphasic in Lead I, upright in Leads II and III, with a duration .08 second. Marked differences were noted in the T-waves of this and the preceding tracings.  $T_1$  was now definitely upright instead of diphasic;

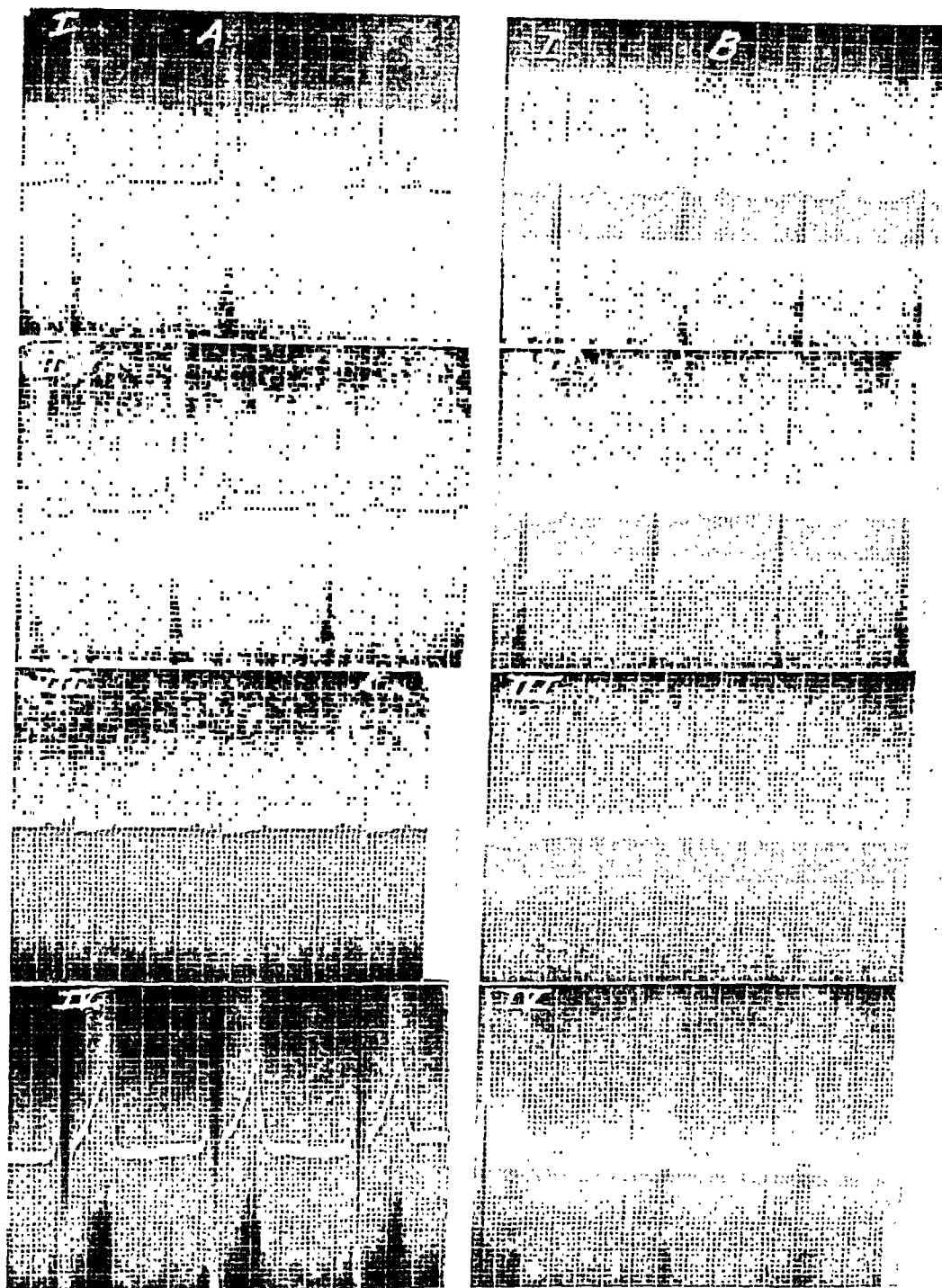


FIG. 2. Case 2. A—original; B—after atropine.  $T_3$  and  $T_{4F}$  show alterations.

$T_2$  remained upright but of reduced amplitude; and  $T_3$  instead of being upright was sharply inverted. The QRS complex in Lead IV-F instead of being entirely upright was now diphasic, and  $T_4$  was now upright rather than inverted. The tracing obtained after exercise was identical with that at rest except for the expected acceleration in rate.

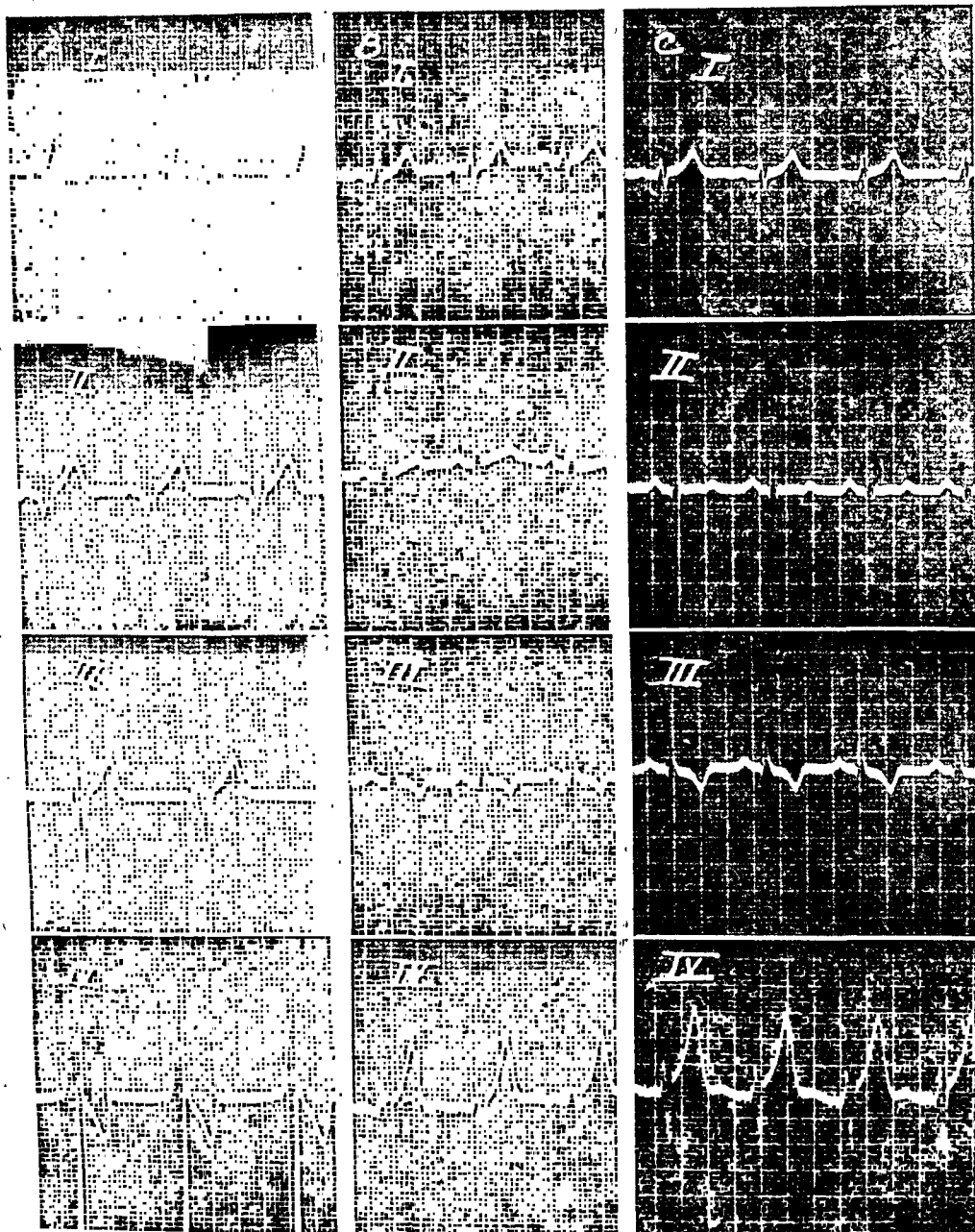


FIG. 3. Case 3. A—original; B—showing spontaneous reversion to normal sinus mechanism; C—sinus rhythm after administration of atropine. Alteration of T-wave is evident in all leads, in both spontaneous and induced reversion.

Electrocardiograms were made at intervals of several days, and in each instance the pattern was the same as on the original examination.

Atropinization with the previously used dosage was repeated, with similar negative result. On another day, after a control tracing to establish the presence at that time of the short P-R interval and prolonged QRS complex, atropinization was carried to the limit of tolerance. In a period of four hours and 40 minutes 1/25 grain was administered by hypodermic in divided doses, in addition to 2/100 grain orally.

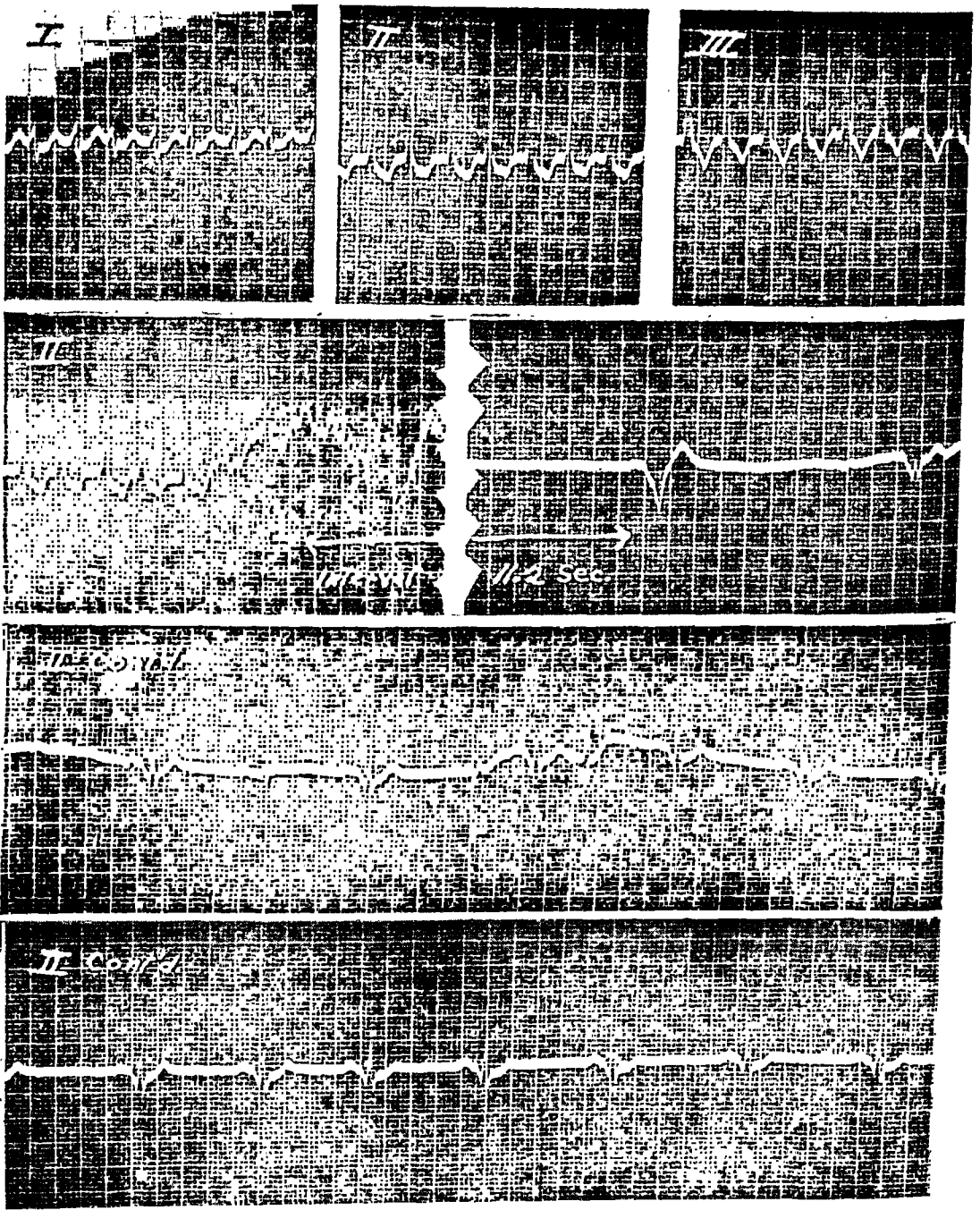


FIG. 4. Case 3. Cessation of tachycardia after ocular pressure. Limb leads above. Lower three strips, except as indicated, are continuous.

Within 30 minutes after the last medication an electrocardiogram was made (figure 3-c). This tracing was identical with that obtained when spontaneous reversion to normal rhythm occurred.

A fast run of 150 yards precipitated an attack of tachycardia of supraventricular type (figure 4). Cessation of the tachycardia was brought about by ocular pressure. Following initial deflections of the beam during pressure there was a period of

asystole which persisted for 11.2 seconds. Cardiac action was resumed with complexes which were irregular both in time and in contour, gradually returning to the characteristic short P-R and prolonged QRS pattern.

*Case 4.* Pvt. J. W., a 36 year old colored soldier with one month of military service, was hospitalized on November 24, 1942. He stated that difficulty was first noted in May, 1940 when he awakened from sleep with palpitation, tachycardia, a choking sensation and precordial oppression. Similar attacks recurred at intervals, with one in September, 1941 more severe than the others, after which bed rest was advised for four months. More recent attacks had been associated with dyspnea, but precordial oppression was noted only if the tachycardia followed exertion.

Past history revealed no illness of note, and venereal infections were denied. Father, mother, and five siblings were alive and well, and there was no incidence of cardiac disease.

Physical examination revealed a good state of development and nutrition. There was definite clubbing of the fingers. The blood pressure was 120 mm. Hg systolic and 90 mm. diastolic. The cardiac rate was 80 per minute, and regular. There were no thrills or murmurs, but the apical first sound was roughened. No other findings of note were present. The size and configuration of the heart and great vessels were normal as determined by fluoroscopy.

Laboratory studies revealed normal findings, except that the original Kahn was reported positive. Two subsequent tests, without therapy, were negative, as was the Wassermann reaction. Erythrocyte sedimentation tests on three occasions were normal.

The electrocardiogram (figure 5-a) on admission resembled bundle branch block of the concordant type. It revealed a regular rate of 75 per minute, P-R interval of .11 second, slurred initial ventricular deflection, and minimum QRS duration of .12 second. RS-T segments were slightly depressed in Leads I and II, in which the T-waves were diphasic, with principal deflection downward.  $T_3$  was inverted, while  $T_{4-F}$  was upright.

On December 11, after administration of atropine gr. 1/100 three times daily for three days (which produced symptoms of atropine effect) an electrocardiogram revealed a rate of 70 per minute, P-R interval of .08 to .10 second in different leads, and QRS duration of .10 to .14 second. The only significant alteration was seen in  $T_{4-F}$  which became dome shaped and of decreased amplitude. On the following day the contour of the positive  $T_{4-F}$  had returned to that of the original tracing. Two extrasystoles were noted (figure 5-d). One of them showed an even shorter P-R interval which measured .08 second, and a QRS, which, though similar to the usual complexes, was decidedly wider, measuring .15 second. This conforms to the description of auricular extrasystoles occurring in this syndrome, as reported by Wolferth and Wood.<sup>5</sup> The second extrasystole appears to be of ventricular origin.

Atropinization, using the same schedule, was repeated after an interval of one week. Examination after this period of medication (figure 5-b) revealed no alteration of P-R interval or of QRS duration, but it was found that  $T_1$  and  $T_2$  had become upright.  $T_3$  showed little change, and  $T_{4-F}$  was of markedly decreased amplitude and altered contour.

Three days later the patient complained that he was having an "attack," and the pulse was found to be quite irregular with the rate recorded as 40 per minute. The apical rate approached 200 per minute but was also irregular. This irregularity was reflected in the sphygmomanometer, the blood pressure varying with each beat. The soldier was uncomfortable, but in no great distress, and walked into the ward office to report his condition. Carotid sinus and ocular pressure were ineffectual. Auricular fibrillation was suspected, but treatment, except sedatives, was withheld pending electrocardiographic study. The tachycardia persisted for four hours, and ceased



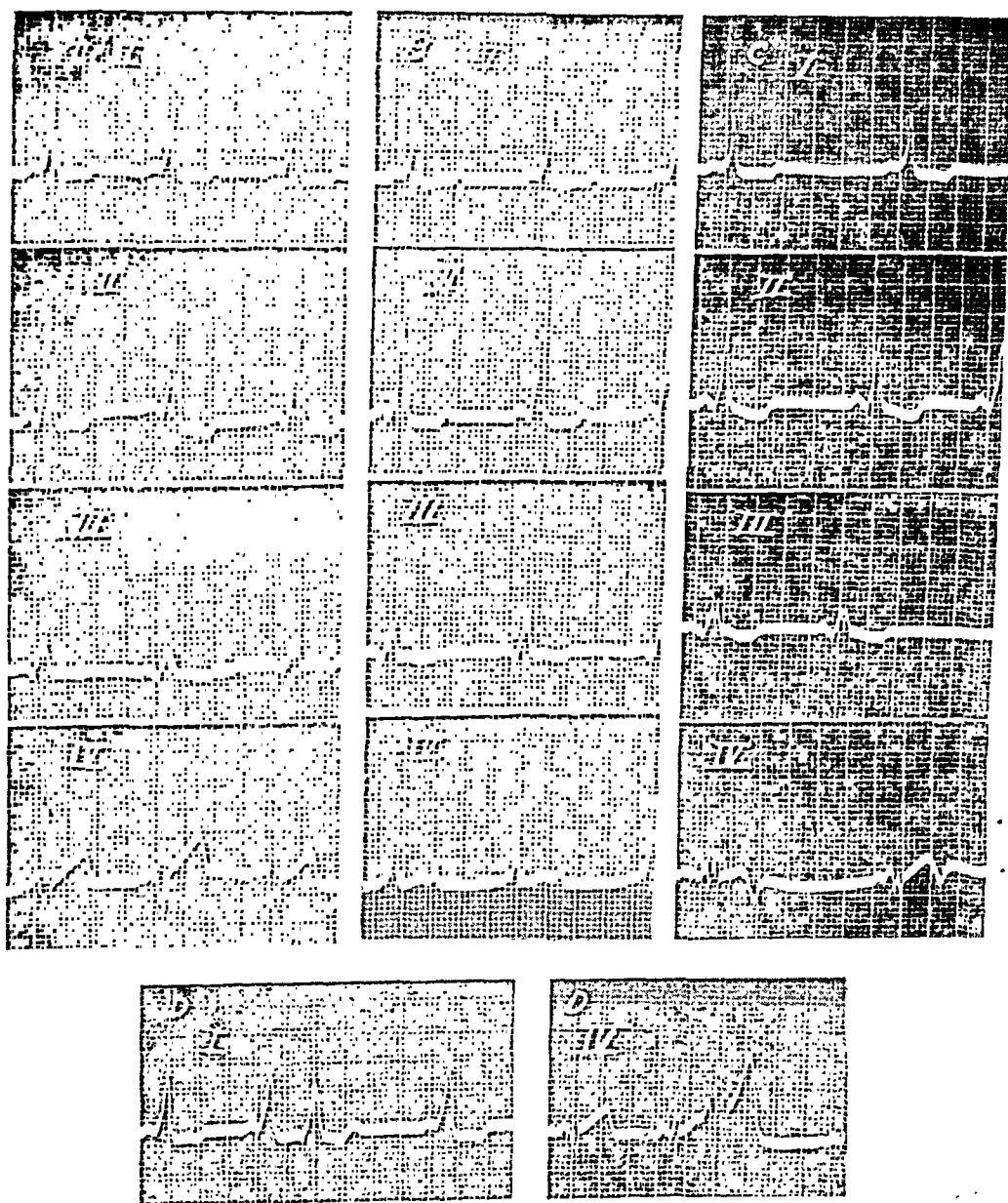


FIG. 5. Case 4. A—original; B—after atropine; C—after digitalis; D—supraventricular extrasystole in Lead I, ventricular extrasystole in Lead IV-F.

after spontaneous emesis. The electrocardiogram (figure 6-a) revealed that the attack had not been auricular fibrillation, but rather, ventricular tachycardia. On the following day the electrocardiogram (figure 6-b) revealed the Wolff-Parkinson-White pattern, but it was noted that T-waves were inverted in all leads, and QRS Lead IV-F was of an entirely different form. Several observers felt that the episode of the previous day had resulted from coronary occlusion, but there was nothing in the subsequent clinical course, febrile reaction, leukocyte count, or erythrocyte sedimentation rate to substantiate such a position. A tracing one month later (figure 6-c) revealed a pattern which was similar to that obtained on the day following tachycardia, except that  $T_{4-F}$  was upright.

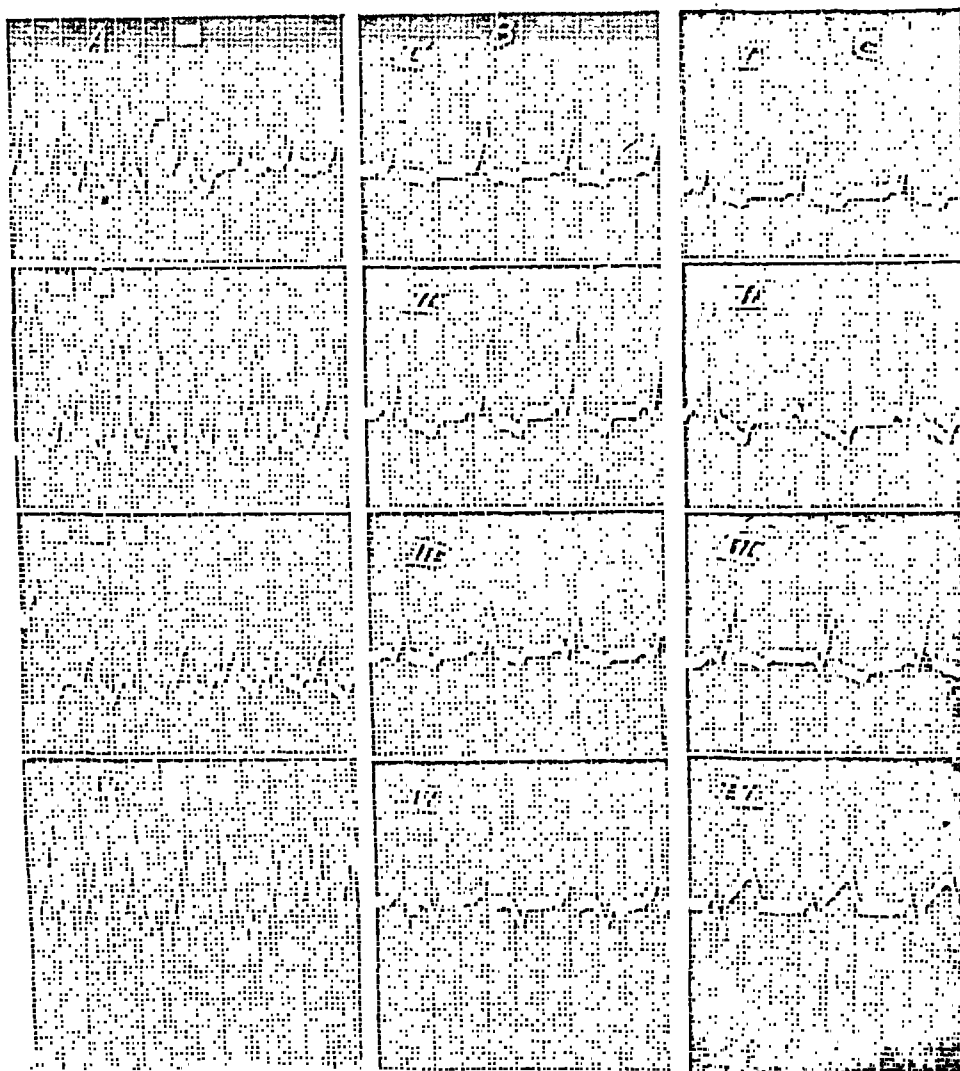


FIG. 6. Case 4. A—ventricular tachycardia; B—tracing obtained on following day; C—electrocardiogram after period of one month.

Following a control tracing several weeks later, which was identical with the original, the patient was fully digitalized, being given 27 grains of the drug in the form of powdered leaf tablets over a period of 26 hours. An electrocardiogram (figure 5-c) 15 hours after the last dose showed no significant changes in the limb leads except bradycardia and respiratory arrhythmia. In the fourth lead the ventricular complexes were of a distinctly different form, and the T-wave was diphasic rather than upright.

#### COMMENT

In addition to the common features previously enumerated these cases demonstrate all the variations so far described in association with the syndrome under discussion. Our fourth case showed a premature contraction which fulfills the criteria of a ventricular extrasystole. Such a complex has not been described in the several articles reviewed.

A most interesting observation has been the marked spontaneous and atropine induced variations in the T-wave. As for the former, case 1 presented at different times, without any medication whatever, T-waves of totally divergent form. These changes were not progressive, but varied from upright, through diphasic, to unquestionably inverted. Hartwell, White, et al. in a recent communication<sup>6</sup> report that, with normal subjects, a lowering of the T-waves in the limb leads is a rather constant finding following atropine. At variance with these results are the alterations in this group of patients with short P-R interval and prolonged QRS. In cases 1 and 4 the diphasic and inverted T-waves in Lead I were made upright. In view of the diagnostic import of marked T-wave changes, these results should be kept in mind. Therefore, to the imposing list, compiled by Sprague,<sup>7</sup> of factors influencing the terminal ventricular complex, atropine should be added. Similar changes may also occur spontaneously in subjects showing the Wolff-Parkinson-White syndrome.

The "paradoxical effect," previously mentioned, consisted of a totally unexpected bradycardia and respiratory arrhythmia after administration of atropine. This effect could not be duplicated in any of the other cases.

Wolferth and Wood<sup>5</sup> quote a case of Scherf and Schönbrunner wherein large doses of digitalis cause the temporary disappearance of the abnormal QRS complexes. Fox, Travell, and Molofsky,<sup>8</sup> on the other hand, report widening of the abnormal QRS complex with the same drug. Apart from the expected S-T changes, full digitalization in one of our cases (4) produced no appreciable effect. Neither the P-R interval nor the duration of QRS was altered.

We were fortunate in securing an electrocardiogram during the termination of an episode of paroxysmal tachycardia by ocular pressure. After asystole the ventricular complexes immediately assumed the Wolff-Parkinson-White form. Since this patient had also shown spontaneous reversion to normal sinus rhythm, we can only speculate as to the mechanism existing at the onset of tachycardia.

The onset of paroxysmal ventricular tachycardia in our last case, associated with marked apprehension, dyspnea, and precordial discomfort, was suggestive of an acute coronary episode, and, in fact, was held to be such by two observers. The possibility of such an error in diagnosis has been pointed out by Levine and Beeson<sup>9</sup> and should be emphasized. In this particular instance the clinical differentiation between paroxysmal ventricular tachycardia and auricular fibrillation was exceedingly difficult. The heart and pulse rates were totally irregular and were uninfluenced by carotid sinus or ocular pressure. There was a marked pulse deficit, and blood pressure was variable as would be expected with auricular fibrillation.

#### SUMMARY

Four cases are reported, exhibiting the syndrome of short P-R interval associated with prolonged QRS complexes in patients with apparently un-

damaged hearts. Features in common with previously described cases are enumerated. All the variations ascribed to this syndrome are demonstrated, except reversion to normal rhythm after digitalis and quinidine.

Paradoxical atropine effects, a ventricular extrasystole, and recovery from auricular paroxysmal tachycardia are recorded.

Spontaneous and atropine induced T-wave changes are emphasized.

# BIBLIOGRAPHY

1. BUTTERWORTH, J. SCOTT, and POINDEXTER, CHARLES A.: Short P-R interval associated with a prolonged QRS complex, *Arch. Int. Med.*, 1942, *lxix*, 437.
2. BISHOP, L. F., JR.: Bundle branch block with short P-R interval in individuals without organic heart disease: case report with review of literature, *Am. Jr. Med. Sci.*, 1937, *cxciv*, 794.
3. HUNTER, A., PAPP, C., and PARKINSON, J.: The syndrome of short P-R interval, apparent bundle branch block, and associated paroxysmal tachycardia, *Brit. Heart Jr.*, 1940, *ii*, 107.
4. WOLFERTH, CHARLES C., and WOOD, FRANCIS C.: The mechanism of production of short P-R intervals and prolonged QRS complexes in patients with presumably undamaged hearts: hypothesis of an accessory pathway of auriculo-ventricular conduction (Bundle of Kent), *Am. Heart Jr.*, 1933, *viii*, 297.
5. WOLFERTH, CHARLES C., and WOOD, FRANCIS C.: Further observations on the mechanism of the production of a short P-R interval in association with prolongation of the QRS complex, *Am. Heart Jr.*, 1941, *xxii*, 450.
6. HARTWELL, A. S., BURRETT, J. B., GRAYBIEL, A., and WHITE, P. D.: The effect of exercise and of four commonly used drugs on normal human electrocardiogram, with particular reference to T wave changes, *Jr. Clin. Invest.*, 1942, *xxi*, 409.
7. SPRAGUE, HOWARD B.: Modern concepts of cardiovascular disease, 1941, *x*, 10.
8. FOX, THEODORE T., TRAVELL, JANET, and MOLOFSKY, LEONARD: Action of digitalis on conduction in the syndrome of short P-R interval and prolonged QRS complex, *Arch. Int. Med.*, 1943, *lxxi*, 206.
9. LEVINE, SAMUEL A., and BEESON, PAUL B.: The Wolff-Parkinson-White syndrome, with paroxysms of ventricular tachycardia, *Am. Heart Jr.*, 1941, *xxii*, 401.

# I. TREATMENT OF EXPERIMENTALLY PRODUCED STAPHYLOCOCCAL THORACIC EMPYEMA\*

By WILLIAM E. EVANS, JR., PH.D., JAMES G. McALPINE, PH.D.,  
BENEDICT SKITARELIC, M.D., and E. HOWARD TONOLLA, M.D.,  
*Baltimore, Maryland*

## I. INTRODUCTION

THE number of cases of thoracic empyema caused by the staphylococci is relatively small, but they present a difficult problem in therapeutics. The sulfonamide compounds have proved efficacious in the treatment of streptococcus infections but in those in which staphylococci play the major rôle, these drugs have not been, as a rule, beneficial. The present war with its multiplicity of gun-shot and shrapnel wounds will undoubtedly contribute its share of thoracic and abdominal empyema, and in a portion of these staphylococci will be present.

The production of staphylococcal empyema in experimental animals has not been very successful in the past although this would be the ideal method of study. After numerous failures a strain of staphylococcus was obtained which upon intrapleural inoculation would consistently cause thoracic empyema in rabbits without setting up a rapidly fatal septicemia. By this method it was possible to make detailed studies on the therapeutic effect of various preparations employing cultural and cytological technics with a terminal necropsy. This paper, which is the first of a series, embraces the study of a number of different combinations of drugs, and has as its objective the determination of those treatments which might be successful.

## II. HISTORICAL

Inasmuch as Graham (1938), Ehler (1941), Carlson (1935-1936) and others have already reviewed the literature on empyema, it seems unnecessary to do so here.

The principles of treatment for thoracic empyema have been outlined by numerous clinicians, but those listed by Harrington (1931) cover the salient points. These are as follows: (1) adequate drainage, (2) avoidance of open pneumothorax, (3) rapid sterilization of the diseased area, (4) early obliteration of the cavity by expansion of the lung.

Menkin (1940), in his monograph on inflammation, has pointed out the sequence of the various phagocytic cells during the process of infection. He

\* Received for publication March 22, 1943.

Funds for the support of this project were made available by the Wallace & Tiernan Products, Incorporated.

From the Departments of Pharmacology, Bacteriology, Pathology and Medicine, School of Medicine, University of Maryland.

has also demonstrated the relationship of hydrogen-ion concentration to the cell picture in the infected area.

The origin and differentiation of the large mononuclear cells, or macrophages, which have been studied by Maximow (1932), Mallory (1914), Evans and Scott (1921), Sabin, Doan and Cunningham (1925), Cunningham, Sabin and Doan (1925), the Lewises (1925, 1926), Foot (1925), Permar (1924) and McJunkin (1919), are not within the scope of this article. It is concluded that all are phagocytic. The experimental studies of Gay and his collaborators (1921, 1926, a, b) on streptococcal empyema have shown the value of cytological examinations in infections of the thoracic cavity.

### III. EXPERIMENTAL

#### *Methods*

1. *Culture.* The strains of *Staphylococcus aureus* which were obtained from human infections did not produce pathological conditions in rabbits. By the courtesy of Dr. J. Howard Brown of The Johns Hopkins University School of Medicine, a culture of the *G.V.S.* strain was obtained. This had been lyophilized since its original isolation in 1926 from a rabbit. In these experiments it was maintained on ordinary agar media without the addition of blood. An attempt was made to control the number of bacteria in order that a localized empyema might be obtained without the production of a fatal septicemia.

2. *The Production of Empyema.* A standard experimental procedure was adopted which was followed in all cases. A space was made in the right pleural cavity by the injection of 20 c.c. of air. Two days later the animal was inoculated with 0.3 to 0.5 c.c. (depending on the estimated number of organisms) of a 24-hour broth culture of *G.V.S.* staphylococcus. Two days after the inoculation, fluid was withdrawn from the pleural cavity. Then 10 c.c. of a solution of the therapeutic agent or agents were injected into and allowed to remain in the space. The treatment was repeated on the next two days. Pleural fluid was again withdrawn three days later. Smears and cultures were made after each aspiration. The animal was then killed with chloroform and the lungs were exposed by cephalad reflection of the pectoral girdle after lateral section of the ribs and transverse section at the level of the diaphragm. A culture of the heart blood was made. After observation of the condition of the pleural cavity, a portion of the right lung was removed for histological study. Specimens of liver and kidney were also removed for examination for possible damage resulting from the drugs used in the treatment. Rectal temperatures were taken in most cases before inoculation, two days after inoculation and on the day of autopsy. The determination of hemoglobin was made by the Sahli method in most cases at the beginning and end of the experiment to ascertain whether bacterial or

drug hemolysis was taking place. Since neither rectal temperature nor hemoglobin varied significantly, these observations were omitted in later experiments.

## MATERIALS

1. *Animals.* Rabbits weighing between two and three kilos were used.

2. *Drugs.* It was deemed desirable to restrict this study of the local treatment of empyema to a few drugs or agents, singly and in many combinations. Therefore, selections were made from classes of substances likely to be beneficial, i.e., immune serum, a chloramine antiseptic, a sulfonamide, and a wetting agent.

Azochloramid (1:3300) prepared from buffered tablets was chosen because it is relatively stable and non-irritating, and, as shown by Heise (1942) is active in vitro against the various staphylococcus toxins.

Sulfanilamide is the only sulfonamide which is appreciably soluble at a neutral hydrogen-ion concentration. An 0.8 per cent solution of this compound was employed.

A 0.2 per cent solution of sodium tetradecyl sulfate, properly neutralized, was used as a wetting agent principally because this compound has had clinical use in the treatment of empyema. The use of wetting agents locally is based on their ability to lower surface tension and thereby, theoretically, facilitate penetration of disinfectants. The literature on wetting agents has been reviewed by Frobisher (1929).

Solutions of these substances were prepared immediately before injection. When combinations of agents were used, solutions were prepared in such manner as to contain them in the foregoing concentrations.

3. *Immune Sera.* In order to produce an antibacterial serum for therapeutic purposes several groups of animals were injected intravenously with the living washed culture. It was thought that the living organisms were to be preferred for this purpose because there is no change in the antigenic structure. The rabbits were injected on two or three alternate days with varying amounts of the washed culture. Twenty-four hour broth cultures were centrifuged and brought to their original volumes with physiological salt solution. The usual dosages were 0.1 and 0.25 c.c. In two or three days the rabbits showed the effects of a generalized infection, i.e., emaciation and osteomyelitis. As a matter of expediency, that the animals might survive for bleeding purposes, intraperitoneal injections of one of the sulfonamides were given. In this way they were kept alive so that they might be bled on the twelfth and fourteenth days following the initial injections. Fatal bleedings were made from the heart, the serum separated, passed through a Seitz filter and preserved under aseptic conditions. The agglutination titer was 1-800. This immune serum was used in a 1:10 dilution.

Lederle's concentrated and refined antistaphylococcic serum in a dilution

TABLE I

Treatment	No. Rabbits		Pleural Fluid: Days after Treatment				Blood after 5 Days
			0	1	2	5	
Controls	8	Culture	+++			++++	+
		Smear	P <sub>4</sub> S D M <sub>1</sub> Ic <sub>3</sub> Ex <sub>3</sub>			P <sub>3</sub> S D M <sub>1</sub> Ic <sub>1</sub> Ex <sub>2</sub>	
A + SA	6	Culture	++++	++++	+++	++	< +
		Smear	P <sub>3</sub> S D M <sub>1</sub> Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>4</sub> S D M <sub>1</sub> Ic <sub>3</sub> Ex <sub>2</sub>	P <sub>1</sub> D S M <sub>occ.</sub> Ic <sub>3</sub> Ex <sub>1</sub>	P <sub>2</sub> D S M <sub>3</sub> Ic <sub>3</sub> Ex <sub>2</sub>	
A + T	6	Culture	+++	+++	+++	+	+
		Smear	P <sub>2</sub> S D M <sub>occ.</sub> Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>4</sub> S D N Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>3</sub> S D M <sub>occ.</sub> Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>2</sub> S D M <sub>occ.</sub> Ic <sub>2</sub> Ex <sub>2</sub>	
IS	6	Culture	++	+++	+++	++	< +
		Smear	P <sub>1</sub> D S M <sub>occ.</sub> Ic <sub>1</sub> Ex <sub>2</sub>	P <sub>2</sub> D S M <sub>2</sub> Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>3</sub> D S M <sub>2</sub> Ic <sub>3</sub> Ex <sub>2</sub>	P <sub>3</sub> S N M <sub>2</sub> Ic <sub>3</sub> Ex <sub>2</sub>	
IS + FS	4	Culture	+++	+++	++	++	0
		Smear	P <sub>1</sub> D Ex <sub>3</sub>	P <sub>4</sub> S D M <sub>2</sub> Ic <sub>3</sub> Ex <sub>3</sub>	P <sub>4</sub> S N M <sub>2</sub> Ic <sub>3</sub> Ex <sub>1</sub>	P <sub>occ.</sub> Bacteria rare	
IS + A	8	Culture	++++	+++	++	+	< +
		Smear	P <sub>4</sub> S D M <sub>occ.</sub> Ic <sub>2</sub> Ex <sub>3</sub>	P <sub>2</sub> S Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>3</sub> S D M <sub>occ.</sub> Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>1</sub> S M <sub>1</sub> Ic <sub>1</sub> Ex <sub>1</sub>	
IS + A + SA	8	Culture	+++	+++	+++	++	+
		Smear	P <sub>2</sub> S D M <sub>2</sub> Ic <sub>3</sub> Ex <sub>2</sub>	P <sub>3</sub> S D M <sub>2</sub> Ic <sub>3</sub> Ex <sub>1</sub>	P <sub>2</sub> D M <sub>2</sub> Ic <sub>3</sub> Ex <sub>2</sub>	P <sub>2</sub> D M <sub>2</sub> Ic <sub>3</sub> Ex <sub>2</sub>	
IS + A + SA + T	6	Culture	+++	+++	+++	< +	< +
		Smear	P <sub>3</sub> S D M <sub>1</sub> Ic <sub>3</sub> Ex <sub>2</sub>	P <sub>3</sub> D S M <sub>2</sub> Ic <sub>2</sub> Ex <sub>1</sub>	P <sub>3</sub> S D M <sub>1</sub> Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>2</sub> D S M <sub>1</sub> Ic <sub>3</sub> Ex <sub>1</sub>	
T	4	Culture	++	+++	++	++	++
		Smear	P <sub>3</sub> N D M <sub>occ.</sub> Ic <sub>1</sub> Ex <sub>1</sub>	P <sub>2</sub> N S Ic	P <sub>1</sub> N D Ic <sub>2</sub> Ex <sub>2</sub>	P <sub>1</sub> N M <sub>occ.</sub> Ic Occ. Ex <sub>2</sub>	

## KEY TO TABLE I

A.....	Azochloramid (1 : 3300)
SA.....	Sulfanilamide (0.8%)
T.....	Sodium Tetradecyl Sulfate (0.2%)
IS.....	Immune Serum (1 : 10)
FS.....	Fresh Serum (1 : 10)
P.....	Polymorphonuclears
S.....	Swollen
D.....	Disintegrated
N.....	Normal
M.....	Macrophages
Ic.....	Intracellular Bacteria
Ex.....	Extracellular Bacteria
Occ.....	Occasional

Subscript numbers refer to number on a 4 plus basis.

of 1 : 30 was used in other cases and did not appear to differ in effect from the serum prepared from the *G.V.S.* strain.\*

4. *Complement.* Since it was found that the pleural exudates were very poor in complement, it was decided to add an equal amount of fresh serum

\* This serum was supplied by the Lederle Laboratories.



to the antistaphylococcic serum. This was obtained by bleeding normal rabbits on the day before other animals were to be subjected to treatment.

### *Presentation of Data*

The cultural and smear studies of the most promising methods of treatment are summarized in table 1.

Other methods of treatment employed were:

No. of Animals	Preparation
2 .....	Azochloramid
2 .....	Azochloramid, sulfanilamide, and sodium tetradecyl sulfate
2 .....	Azochloramid, sodium tetradecyl sulfate, and immune serum
2 .....	Normal serum
2 .....	Normal serum and azochloramid
3 .....	Normal serum, azochloramid, and sulfanilamide
6 .....	Sodium tetradecyl sulfate, and immune serum
2 .....	Sulfanilamide
2 .....	Sulfanilamide and immune serum
2 .....	Sulfanilamide and sodium tetradecyl sulfate

*Gross Study.* Necropsies were performed on all the animals at the end of seven days. On the treated side all showed atelectasis and a white thick shaggy exudate in varying amounts. Those treated with sodium tetradecyl sulfate contained particularly large amounts of fibrin. Adhesions were present in varying degrees between the visceral and parietal pleurae. There was a serous blood tinged pleural effusion on the contralateral side in three of the animals.

Sections of the lungs, the kidneys, and the liver were removed for microscopic study.

*Microscopic Study.* The kidneys and livers showed no significant lesions. The lungs in general were atelectatic in varying degrees in all cases, the compression usually being in direct proportion to the amount of exudate present. The pleurae were slightly thickened and displayed many small dilated capillaries. Some subpleural pneumonitis was present in all cases, as evidenced by polymorphonuclear infiltration deep in the interstitial tissue. Most of the lungs were moderately congested. The alveoli and the bronchi remained clear; there was no evidence of a pneumonic process except for the above mentioned subpleural involvement.

The pleural exudate of all the controls was loaded with polymorphonuclears, and there were many small areas of abscess formation present. No fibrin was seen. Atelectasis was almost complete.

The animals treated with azochloramid and sulfanilamide showed moderate amounts of fibrinous exudates which contained mainly polymorphonuclear leukocytes. These cells also invaded the interstitial lung tissue in varying numbers. Few mononuclear phagocytes were seen.

The animals treated with azochloramid and sodium tetradecyl sulfate showed varying amounts of fibrin in which were seen only small scattered

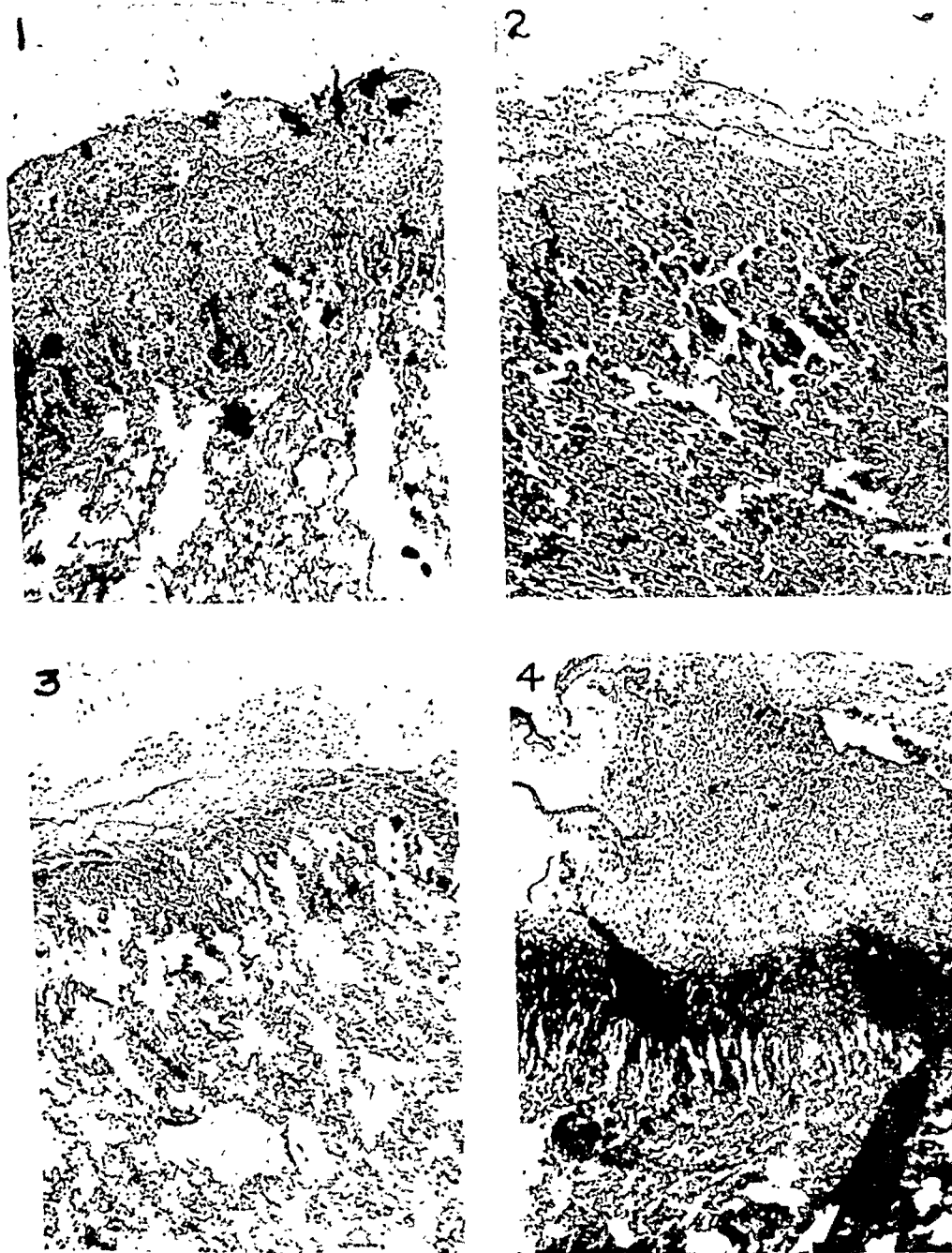


FIG. 1.

1. Control

3. Sodium tetradecyl sulfate

2. Azochloramid and sodium tetradecyl sulfate

4. Immune serum

wandering cells, most of which were polymorphonuclears. There was a slight fibroblastic proliferation on the visceral pleura. The lung parenchyma showed no change.

The animals treated with immune serum revealed a moderate amount of fibrinous exudate which was moderately infiltrated with polymorphonuclears.

The animals treated with immune serum and fresh serum contained a moderate amount of exudate in which the mononuclear phagocytes predominated. Much of the exudate was acellular. Only an occasional polymorphonuclear was seen.

The animals treated with immune serum and azochloramid showed small amounts of fibrin; the polymorphonuclear and monocytic forms were about equally distributed.

The animals treated with immune serum, sulfanilamide, and azochloramid contained only a scant amount of fibrin in the exudate. Most of the cells were disintegrated.

The animals treated with immune serum, azochloramid, sulfanilamide, and sodium tetradecyl sulfate showed little pleural exudate which contained a few polymorphonuclear and mononuclear phagocytes in its meshes. For the most part the lungs were completely collapsed and the pleura was covered with a scant amount of fibrin. There was an increased amount of subpleural pneumonitis present.

The animals treated with sodium tetradecyl sulfate showed a moderate amount of fibrin and a fibroblastic proliferation of the pleura. The mononuclear phagocytes were predominant.

#### IV. DISCUSSION

The short treatment period was decided upon in order to eliminate the greater number of the possible therapeutic agents and combinations of agents from further consideration. An exhaustive study of the remainder would then be practical. It was realized that complete sterilization of the cavity could not be attained within such a short period. Selections were based on culture studies, smears of the pleural exudates, gross findings on autopsy, and histological studies of the lung and pleura on the treated side.

The cultures obtained from the untreated animals showed an increase in bacterial content during the experimental period. In all the other selected groups there was a diminution in the estimated number of microorganisms to 1-2 plus on the day of necropsy. Blood cultures with the exception of those animals treated with sodium tetradecyl sulfate were never over 1 plus. Inasmuch as the amount of fluid which could be aspirated from some animals was relatively small, direct bacterial counts were not attempted. The standard procedure was to place three drops of the aspirated fluid on an agar slant and incubate for 48 hours. The number of bacteria which had appeared at that time was recorded on the 4 plus basis. For the blood cultures the same technic was adopted.

Smears on the first day before treatment, i.e., 48 hours after infection, showed large numbers of polymorphonuclear leukocytes, mostly swollen, some disintegrated, and occasional macrophages. At this stage of the

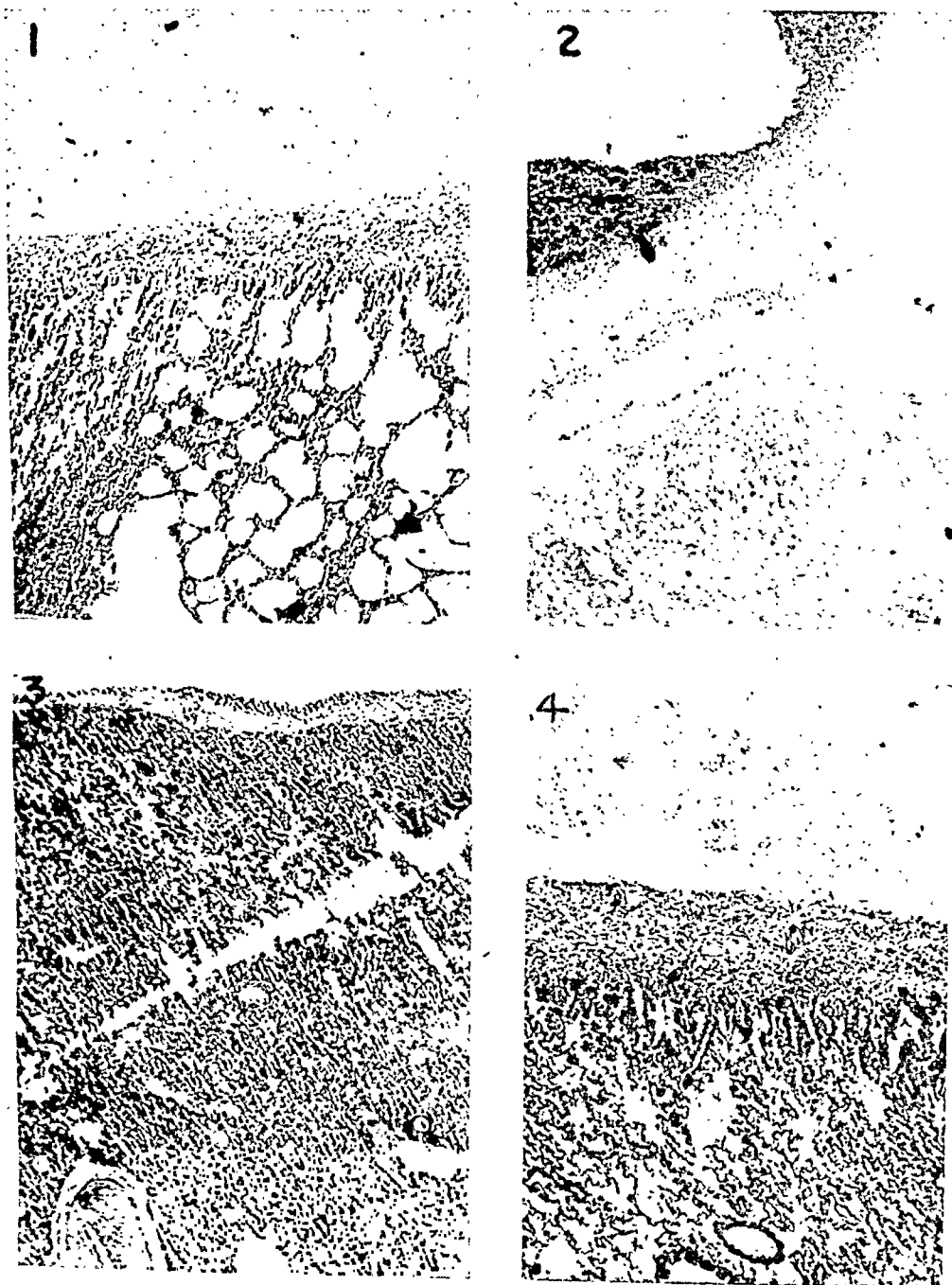


FIG. 2.

1. Immune serum, azochloramid, sulfanilamide and sodium tetradecyl sulfate  
3. Immune serum and azochloramid

2. Azochloramid and sulfanilamide  
4. Immune serum and fresh serum

infection phagocytosis was relatively good. In the controls on the final day the phagocytosis was less and the bacteria more numerous extracellularly. The pleural smears of the animals treated with azochloramid and sulfanil-

amide were similar to those which had been treated with azochloramid, sulfanilamide and immune serum, showing fairly large numbers of macrophages on the final day and a 3 plus phagocytosis. The exudates of those receiving azochloramid and sodium tetradecyl sulfate contained large numbers of polymorphonuclear leukocytes, with occasional macrophages. The bacteria were approximately equally distributed intra- and extracellularly, and the latter appeared to be enmeshed in fibrin. There was little phagocytosis when sodium tetradecyl sulfate was used alone. The animals treated with sodium tetradecyl sulfate, azochloramid, sulfanilamide and immune serum showed in their pleural exudates disintegrated polymorphonuclears with excellent phagocytosis. When immune serum and azochloramid were employed, the numbers of polymorphonuclears were small, and though swollen their condition was otherwise excellent. The infectious process showed favorable progress. In those animals treated with immune serum alone the exudates exhibited good phagocytosis. The combination of fresh serum with immune serum appeared to give the best results in the series. The infectious process had cleared to such an extent that only a few cells were present.

Gross findings showed that those animals treated with fresh serum and immune serum responded well. The cavities were clear and the exudates were minimal, agreeing with the foregoing cytological and cultural results. Others showed varying amounts of infection and exudates which were also comparable to the above discussed results.

Microscopically the controls all showed a great amount of exudate, rich in inflammatory cells, the predominating form being the polymorphonuclears. In those treated with azochloramid and sulfanilamide there were moderate amounts of fibrinous exudate containing many polymorphonuclears. This process was still active after five days of treatment. Where azochloramid, sulfanilamide and immune serum were employed the sections showed the presence of thick fibrin and many disintegrating polymorphonuclear and mononuclear cells. On the whole this process appeared favorable. In the series in which azochloramid and sodium tetradecyl sulfate were used no great amount of fibrin appeared in the sections, although it was very noticeable in the gross findings. It may have been stripped off with ease since fibroblastic proliferation was seen on the pleura. In the inoculated animals sodium tetradecyl sulfate produced a moderate cellular response and an outpouring of fibrin. The series in which sodium tetradecyl sulfate, azochloramid, sulfanilamide and immune serum were employed showed very little exudate, and there were only a few inflammatory cells present in its meshes. A favorable result was evidenced in this series. In animals treated with immune serum and azochloramid, the sections showed a small amount of fibrin and the polymorphonuclear and mononuclear forms were about equally distributed; only one animal exhibited a residual infection as shown by the presence of a relatively few inflammatory cells. Where immune serum

alone was used the polymorphonuclear response was great, fibrin was scant, and several animals were practically free from exudates. In sections from those animals treated with fresh serum and immune serum, the exudate was scant and practically acellular with mononuclear forms predominating and only occasional polymorphonuclears.

Representative photomicrographs of each series are appended.

## V. SUMMARY AND CONCLUSIONS

This problem was limited to the study of pleuritis produced by a special strain of *Staphylococcus aureus*. No other organisms have been used.

The following possibilities are suggested:

1. Immune serum alone appeared to stimulate an earlier and greater response on the part of the mononuclears and the animals were obviously benefited.

2. Immune serum with complement also produced an early and active response on the part of the mononuclears. Phagocytosis was more marked, and by the seventh day bacteria were either markedly reduced or absent. Little exudate remained.

3. In other cases in which azochloramid was used in combination with other agents the results in general were: increased phagocytosis in some cases, and increased exudate of serum and fibrin in other cases. The fibrin in the latter showed favorable lysis and the fibroblastic proliferation in the pleura was scant.

4. The reactions in the animals treated with sulfanilamide, sodium tetradecyl sulfate, and azochloramid, were more favorable than in the controls, but less favorable than in the immune serum-complement series.

5. Those methods of treatment which appear to merit further study are: (1) azochloramid and sulfanilamide, (2) azochloramid and sodium tetradecyl sulfate, (3) immune serum and fresh serum, (4) immune serum and azochloramid.

## BIBLIOGRAPHY

- CARLSON, H. A.: Acute empyema thoracis. A study of healing and pulmonary expansion, Jr. Thor. Surg., 1935-1936, v, 393.
- CUNNINGHAM, R. D., SABIN, F. R., and DOAN, C. A.: The development of leucocytes, lymphocytes, and monocytes from a specific stem cell in adult tissue, Contrib. to Embryol., Carnegie Inst. Washington, 1925, xvi, 27.
- EHLER, A. A.: Non-tuberculous thoracic empyema. A collective review of the literature from 1934 to 1939, Surg., Gynec., and Obst., 1941, lxxii, 17.
- EVANS, H., and SCOTT, K.: On the differential reaction to vital dyes exhibited by the two great groups of connective tissue cells, Contrib. to Embryol., Carnegie Inst., Washington, 1921, x, 1.
- FOOT, N.: The endothelial phagocyte. A critical review, Anat. Rec., 1925, xxx, 15.
- FROBISHER, M., JR.: Studies upon the relationship between surface tension and the action of disinfectants with special reference to hexyl-resorcinol, Jr. Bact., 1927, xiii, 163.

- GAY, F. P., and MORRISON, L. F.: Experimental streptococcus empyema, Jr. Infect. Dis., 1921, xxviii, 1.
- GAY, F. P., and CLARK, A. R.: The bactericidal action of pleural exudates, Arch. Path. and Lab. Med., 1926, i, 847.
- GAY, F. P., and CLARK, A. R.: A histologic basis for local resistance and immunity to streptococci, Arch. Path. and Lab. Med., 1926, i, 857.
- GRAHAM, E. A.: Some accomplishments of thoracic surgery and its present problems, Surgery, 1938, iii, 485.
- HARRINGTON, S. W.: The surgical treatment of acute empyema, Minnesota Med., 1931, xiv, 1042.
- HEISE, MARGARET D.: The effect of disinfectants on staphylococcus coagulase, hemolysin, dermonecrotizing toxin, and lethal toxin, 1942, The Ohio State University: Abstracts of Doctoral Dissertations. No. 36.
- LEWIS, M.: The formation of macrophages, epithelioid cells and giant cells from leucocytes in incubated blood, Am. Jr. Path., 1925, i, 91.
- LEWIS, W.: Macrophages of the deep fascia of the thigh of the rat in spreads supravitality stained with neutral red and with janus green, Anat. Rec., 1926, xxxii, 215.
- MALLORY, F.: The principles of pathologic histology, 1914, W. B. Saunders Co., Philadelphia.
- MAXIMOW, A. A.: The macrophages or histiocytes. In Special Cytology (E. V. Cowdry, Editor), Paul B. Hoeber, Inc., New York, vol. ii, p. 711.
- MCJUNKIN, F.: The origin of the phagocytic mononuclear cells of the peripheral blood, Am. Jr. Anat., 1919, xxv, 27.
- MENKIN, VALY: Dynamics of inflammation, 1940, The Macmillan Co., New York.
- PERMAR, H.: The function of the endothelial cell in pathological conditions, especially in tuberculosis, Am. Rev. Tuberc., 1924, ix, 507.
- SABIN, F., DOAN, C., and CUNNINGHAM, R.: Discrimination of two types of phagocytic cells in the connective tissues by the supravital technique, Contrib. to Embryol., Carnegie Inst. Washington, 1924, xvi, 125.

# SPONTANEOUS COMPLETE RUPTURE OF THE AORTA WITHOUT DISSECTING ANEURYSM, WITH REPORT OF A CASE SHOWING A NEW PHYSICAL SIGN (PERIAORTIC FRICTION RUB) \*

By FREDERICK R. TAYLOR, M.D., F.A.C.P., *High Point, N. C.*, and ROBERT  
P. MOREHEAD, M.D., *Winston-Salem, North Carolina*

## INTRODUCTION

RUPTURE of the aorta is by no means rare. Until comparatively recently, the commonest cause was probably a syphilitic aneurysm. With modern methods in the treatment of syphilis, however, such aneurysms have become much less common than formerly.

The causes of complete rupture of the aorta may be classified as follows:

1. Major trauma. This may be a direct piercing injury, as from a bayonet, bullet, etc.; or a severe, non-penetrating, crushing injury to the chest, such as occurs when a person is injured by a "cave-in" or falls from a high place.

2. Minor trauma combined with one of the factors listed below. When the aorta is "ripe" for "spontaneous" rupture, a relatively light blow on the chest or back, a fall from a horse, or a sudden strain, caused by lifting a heavy object or straining at stool, may precipitate the rupture. Several cases of aortic rupture during labor have been reported, especially in the German literature.<sup>5</sup>

3. Syphilis of the aorta, usually aneurysm, occasionally a simple syphilitic aortitis.

4. Atherosclerosis of the aorta with gross necrotic areas in the wall.

5. Mycotic aneurysms.

6. Extrinsic disease, such as tuberculosis, malignancy, septic processes, etc., damaging the aortic wall by extension, with or without thrombosis.

7. Coarctation, often associated with mycotic aneurysms.

8. Congenital hypoplasia of the aorta.

9. A condition in which the aortic wall is of paper-like thinness.

10. Dissecting aneurysm independent of any of the above factors (except minor trauma, which may be present or absent).

11. A condition where no gross change can be observed in the aortic wall.

In the cases associated with major trauma, syphilitic aneurysm and congenitally thin aortic wall, the mechanism of rupture is obvious. In all the

\* Received for publication February 25, 1943.

From the Departments of Internal Medicine and Pathology of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.



other types of rupture, except those due to syphilitic aortitis and those in which there is no gross change in the vessel wall, it is usual for a dissecting aneurysm to be formed before complete rupture occurs. Hypertension is often an important additional factor, and is practically always present in cases of coarctation above the stricture, where the rupture occurs.

Even excluding major trauma and syphilitic aneurysm, the literature on spontaneous rupture of the aorta, usually with associated dissecting aneurysm, is quite voluminous, far more so than the files of clinical and pathological journals would suggest. Although a considerable number of articles on the subject may be found in such journals, it is in the anatomical literature, especially in that of France, that one finds the greatest wealth of material. One publication, *Bulletin et Mémoires de la Société Anatomique de Paris*, going back for over a century, lists more than 50 articles on spontaneous rupture of the aorta, usually with dissecting aneurysm. One of us collected a bibliography of some 300 articles on the subject, about one-third of which he was able to verify personally. As the subject of this paper excludes dissecting aneurysm, it seems unwise to occupy space with such an extensive list of references, most of which have no special bearing on our subject. All the articles which could be verified on spontaneous rupture without gross defects in the vessel wall at the point of rupture will, however, be listed, as well as a few others having some special bearing on this paper.

*Some Previous Clinical Observations.* According to Bright,<sup>6</sup> Vesalius suspected that ruptures of non-aneurysmal aortas occur and predicated them without any clinical evidence.

Morgagni<sup>30</sup> reported several cases of rupture of the aorta in his famous work on the seats and causes of disease, first published in 1761. Some of these were associated with ordinary aneurysms, some with dissecting aneurysms; but in two cases no obvious disease of the aorta is mentioned, though minor trauma occurred in one of them. In Letter XXVI he treats "of sudden Death, from a Disorder of the sanguiferous vessels, especially those that lie in the Thorax." In that letter we find the following:

"6. But the great artery is sometimes eroded, even without an aneurysm, and pours out its blood, as the next very short history teaches.

"7. A certain man was taken off by a sudden death, in the latter end of June, in the year 1689. Permission being obtained, with great difficulty, from the relations to dissect the body, the aorta was found to be ruptured where it was nearest to the heart; and the pericardium was from thence quite full of coagulated blood."

In Letter LIII, Art. 35, we read:

"An old man, being busy in cutting wood in the forest of another person, was caught by the master of the forest in the middle of his theft. The master first blamed him, which was answered from the old man by curses and threats; and at length, as the old man was running away, the master struck him on the back, only once, with a club. The man fell down dead from the blow, after going two or three paces.

"The great artery was found to be ruptured transversely, and cleft asunder; notwithstanding the vertebrae and ribs were sound and unhurt."

The next description of a case of rupture of the aorta without mention of any evidence of dissecting or other aneurysm which we have been able to find in the

literature is that of Rose<sup>37</sup> in 1828. This was the case of a 65 year old man, tall and strong, who had had chronic rheumatic pains, but whose health seemed otherwise good. Fifteen days after his general good health had been established by an examination, he got into a violent argument and felt a sudden intense pain beginning in his chin and radiating along the great vessels of his neck, down into his chest and back. It was so severe that he had to lie down in the field. The pain lasted through the night and into the next day, when Rose saw him. At this time he was lying supine, his arms stretched out at his sides, avoiding the slightest movement. His pulse varied from 96 to 100 per minute. His tongue was moist, with a brownish tint to its central part; his face showed suffering; his respiration was easy, but the pain, especially in his back, increased, and from time to time went through his chest. The day after this his pain was much less, and he enjoyed bouillon. At 8 p.m., however, he displayed great agitation and "obstinate tenesmus" (whether vesical or rectal, the account does not state). At 9 p.m. his pain was worse, he changed his position constantly, his pulse was weak and irregular, he had a generalized cold sweat and seemed moribund. He responded to stimulation, but at 4 o'clock the next morning, on trying to get up and go to the toilet, he suddenly died. In the arch of the aorta, on the concave side, was a slit, the edges of which showed no sign of ulceration. There was an enormous clot in the posterior mediastinum and between the lungs and pleurae, with marked infiltration into the thoracic intercellular tissue.

A third case of interest is that of DeAngelis<sup>2</sup> in 1836, for it is the first report known to us in which the patient was stated to be a relatively young person. Here, in a 35 year old man, moderate trauma may or may not have been a factor, for he fell from a ladder "about the height of a man." About an hour later, after eating as usual, he remarked on getting up from the table that the fall had not hurt him. He got back on the ladder and resumed his work of picking olives. In the evening he went home, carrying the ladder on his back. On getting home, he felt sick and had to go to stool. After defecating, he fell dead. An enormous amount of blood was found in his left pleural cavity. This had separated into clot and serum, the total amount weighing about seven pounds. There was a tear in the descending aorta at the level of the seventh rib. The pericardium, heart and lungs were healthy.

Sibley's case,<sup>39</sup> reported in 1864, is of some special interest because of the extraordinary pathological findings. The absence of a dissecting aneurysm in the ruptured aorta, and the presence of one elsewhere, make the case unique. The patient was a messenger aged 53, of small stature, stout and florid. His previous history was negative save for occasional "bilious attacks." He went one evening to wait on a dinner table. In the kitchen he complained of gaseous distention with inability to get up the gas, and asked for some brandy and potash water. He was speaking cheerfully and was turning to go out of the kitchen, when he fell down, gave one or two gasps, and died. At necropsy the pericardium was found to be distended with dark fluid and contained a pound of coagula with about an equal amount of liquid. The pericardium itself was healthy save for a slit where it was reflected over the great vessels. The heart was rather large and pale. The valves were healthy except for slight traces of atheroma. The aorta was considerably dilated, and a large transverse rent was found, involving fully two-thirds of the circumference of the aorta, about an inch above the aortic valves. The rupture extended through the whole substance of the vessel, which showed no dissecting aneurysm. There was some atheroma, but it was neither extensive nor advanced. There was, however, a dissecting aneurysm in the subclavian artery, but this apparently had nothing to do with the rupture of the aorta.

In Browning's case<sup>8</sup> of a 34 year old blacksmith, reported in 1871, in which rupture occurred into the pericardium with instant death, the rupture "was attributed

to the giving way of a small atheromatous spot," but whether this was an observation or an assumption is not clear.

In 1892 Brouardel and Vibert<sup>7</sup> reported a unique case of rupture due to a remarkable condition which could not be detected clinically. As we know of no other such case on record, it is summarized for its historical value, and also to illustrate the ninth heading in our classification of causes of ruptured aorta. The patient was a 20 year old medical student. He had had some minor convulsions in the first year of his life, and a very severe case of typhoid fever at the age of five years, when he "hung between life and death for three months." He had no illness thereafter until his final one, and had been active, worked hard, run with his comrades, and had had no dyspnea, palpitation, syncope or hemorrhages. After a day's work in the dissecting room he went home about 8 p.m., wrote a gay letter to a friend and went to bed. That night he felt abdominal pain and said he had colic. He went to the toilet at 4 a.m., but had no diarrhea. His pains persisted and localized in the liver region. Dr. Collardeau saw him at 8 a.m., thought of the possibility of "hepatic colic," and prescribed a purge followed by laudanum, and a potion. About noon Dr. Collardeau found the patient's pains worse and the bilious vomiting persisting. At 6 p.m. the pain was much worse, forcing the patient to cry out. At 7 p.m. he asked for some lemonade, then suddenly sat on his bed, cried out twice, seized his mother's arm, squeezed it hard for only a moment, and then fell dead. At necropsy the right pleural cavity was found to contain 250 grams of uncoagulated blood. There was also a large pocket containing 1800 grams of liquid and coagulated blood which communicated with the posterior mediastinum, the cellular tissue of which was infiltrated with coagulated blood. The lungs were normal. The pericardial cavity contained two coffee cupfuls of reddish liquid. The blood around the aorta extended up to the retropharyngeal cellular tissue, and down to the iliac arteries, on the left side even going "through the crural ring to the emergence of the deep femoral." The aorta showed two transverse ruptures: "one 2½ cm. long, 3 cm. below the beginning of the left carotid; the other 25 mm. long, 3 cm. below the diaphragm." The aortic diameter was small; opened and spread out, the aorta was 42 mm. wide. It was of a paper-like thinness. Under a magnifying glass, little tears became visible in addition to the larger ones. All the other arteries examined, including the left carotid, left femoral and basilar, seemed normal. Histologically, there was complete degeneration of the media. Brouardel and Vibert believed the condition of the aorta to be due either to the severe typhoid fever at the age of five years, or to a congenital anomaly.

Until the opening of the present century, the interest in our subject had been largely anatomical. Since then, however, increasing clinical interest has been taken in spontaneous aortic rupture, and important contributions have been made to our knowledge of the pathology of the condition. In the early part of the present century, very extensive clinical studies were made by Bright,<sup>8</sup> by Gardette,<sup>17</sup> and by Achard and Paiseau.<sup>1</sup> More recently, Hamman<sup>21</sup> has made a brilliant contribution, making an antemortem diagnosis of rupture of the aorta (with or without dissecting aneurysm) from the record of a patient. The most notable contributions to the pathology of the condition appeared in Germany in 1929 and 1931, by Erdheim<sup>14</sup> and Cellina,<sup>9</sup> respectively. In 1932, Moritz<sup>31</sup> gave an able discussion of the subject in the United States. Rochard and Debelly<sup>30</sup> reported a remarkable case occurring at the beginning of a laparotomy, in which the abdominal aorta ruptured, the rupture was sutured, and the patient survived for three

and one-half hours. The blood was found escaping into the peritoneal cavity when the abdomen was first opened.

Kaufmann's patient,<sup>23</sup> a groom aged 19, was admitted to Queen's Hospital, Birmingham, England, almost unconscious. The next day, however, he was able to give his history. For a month previous he had complained of an aching, sometimes shooting pain in the back of his lower chest about the level of the eighth thoracic vertebra, worse on exertion, but not on deep inspiration. He had no cough. Thirteen days before admission a doctor gave him a bottle of medicine without examining him; his pain was relieved and did not trouble him again for 10 days. On its recurrence, the treatment was repeated, this time without benefit. He kept working for the next three days, but then, about 2:30 p.m., soon after dinner, his pain became very much worse. He stopped work and caught an omnibus a few yards away without running for it, and started home. Within five minutes the guard noticed that he looked very ill. He called a physician, who found him collapsed and pulseless, gave him strychnine, and sent him to the hospital. There was no history of chest injury, no cough or indigestion, and no evidence of tuberculosis or syphilis. On admission he was pale, slightly cyanotic, partly conscious, restless and in great pain. His pulse was rapid and very small. His abdomen was rigid, but not distended, and there was no dullness in the flanks. There was considerable tenderness in the right hypochondrium. No abnormal masses were felt. The sternum was prominent, and the left side of the chest hardly moved in respiration. A palpable "apex beat" was noted in the third interspace in the *right* nipple line. The left axilla was dull up to the fifth rib, and above this a low-pitched tympanitic note was obtained, reaching as far to the right as the midline and upwards almost to the clavicle. Behind, the left chest was dull up to the seventh rib, and above this the dullness shaded off to a normal note at the apex. Over the very dull area no breath sounds could be heard, and vocal fremitus was absent. In the hyperresonant area, faint breathing with prolonged expiration was heard, and in the partly dull area, diminished, though rather harsh, vesicular breathing. There was no change in the percussion note over the right lung, and the breath sounds, though harsh, were vesicular. The "anvil sound" (coin sound) was heard well over the third and fourth left interspaces in front. There were no heart murmurs. The temperature was 98.2° F., pulse rate 120, and respiratory rate 28. The day after admission he was still very pale, but fully conscious and less restless. His abdomen was rigid and retracted slightly on inspiration, the recti hardening on expiration. It was tympanitic throughout. At a second examination there was slight tenderness in the left hypochondrium, none elsewhere. The physical signs in the chest were unchanged except that the hyperresonant area extended to the right of the sternum and was of higher pitch than before. As the patient was evidently suffering greatly from increased pressure in the left chest, thoracentesis was done in the fifth interspace in the left anterior axillary line at about the upper limit of dullness. A mercury manometer showed a positive pressure of 35 mm. with expiration. About 2 ounces (60 c.c.) of air and 10 to 12 drams (40 to 48 c.c.) of dark fluid blood were then withdrawn. The intrathoracic pressure fell considerably, but blockage of the cannula and tubes with clots made further measurements unreliable. Just after tapping, the hyperresonant note was much less high-pitched and did not reach quite to the right edge of the sternum.

On the third day after admission, the patient's temperature was 99.6° F., but his general condition was much better. For the first time, a soft systolic whiff was heard at the first left cartilage, and a similar one immediately after the first sound in the third right interspace at the point of maximum pulsation. The rigidity and tenderness of the abdomen had almost entirely disappeared; there was more dullness in the left chest (the whole axilla being dull), but expansion was increasing. Two

days after this the patient was much better, and the chest tympany did not transgress the midline. The upper left chest, as far down as the third rib, gave a loud tympanitic note, thence to the fifth rib a shallow "tubular" note, and below that, absolute dullness. The heart remained as before, but a slight epigastric pulsation, probably representing the true apex beat, was now felt. After another two days, at 9:20 a.m., while apparently doing well, the patient cried out suddenly with pain in his left chest and became blanched and covered with cold sweat. He was given morphine, but died in 20 minutes. During this time the dullness in his left side rose much higher. He had no vomiting in the hospital, and only an occasional short dry cough. The urine only once showed a trace of albumin (the day after admission) and no casts or blood were found in it.

At necropsy, the heart was found to be completely in the right side of the chest, and a large blood clot was found between the front of the left lung and the chest wall, coming from an oblique tear across the descending aorta which must have existed some days, as it showed signs of inflammation and some repair. The aortic wall appeared healthy, but rather thinner than usual.

Some features of special interest occurred in the case of a 44 year old man reported by Achard and Paisseau.<sup>1</sup> While at dinner with his family he was taken violently ill with great dyspnea and was sent to the hospital. On his arrival, his dyspnea had moderated somewhat, but he complained of deep "localized" thoracic pain, and remarked that he felt as if a blood clot were forming in his throat! He had no hemoptysis, was restless and thirsty during the night, and got up several times to drink great quantities of water. In the morning, being unable to rest in bed because of increasing dyspnea, he sat up in a chair. In about half an hour he complained of violent pain, got up suddenly, fell unconscious and died within a few seconds after being carried to his bed. This patient had been an acrobat and weight lifter and had "copiously fêted Venus and Bacchus." His rupture being associated with a dissecting aneurysm, falls outside our group; but the feeling of a clot forming in his throat was so striking that it seems worthy of mention here.

Other contributions from various standpoints are noted in the bibliography.<sup>8, 10, 11, 18, 20, 22, 26, 27, 28, 29, 32, 33, 35, 42</sup>

#### AUTHORS' CASE REPORT

The patient was a 48 year old farmer who, because of a crippled knee, found it difficult to do heavy winter farm work such as logging, and therefore operated a planer in a furniture factory in the winter months. One of us had examined him some 15 months previously, at which time the diagnosis was hypertensive cardiovascular disease, arteriosclerosis, a mild left hemiplegia due to a cerebral vascular accident, which seemed to be improving, and dental sepsis due to pyorrhea, crowned teeth, etc. His blood pressure at that time was 240 mm. Hg systolic and 120 mm. diastolic. His condition steadily improved after dental treatment, so that by January 25, 1941, his blood pressure was 210 mm. Hg systolic and 110 mm. diastolic, he could use his left side quite satisfactorily, and was working regularly.

On January 29, 1942, just as he started to eat lunch in the furniture factory, he had a slight pain under the xiphoid. He consulted a physician who thought he had indigestion and gave him a purgative, though his bowels were quite regular and had moved that morning. He returned to work in the factory. About 4 p.m. he was seized with a very different, agonizing pain, also under the xiphoid. The same physician whom he had seen at lunch time was called, and feared that the patient had had a gastric hemorrhage, though there had been no nausea or vomiting. He advised immediate admission to a hospital. The patient was sent in an ambulance to the

Burrus Memorial Hospital in High Point. On arrival he showed an ashy cyanosis and was obviously suffering extreme pain in the xiphoid region. His pulse was very tense. About 6 p.m. his blood pressure was 212 mm. Hg systolic and 130 mm. diastolic. At 7 p.m. it was 220 mm. Hg systolic and 146 mm. diastolic. At this time his white cell count was 20,400, with 96 per cent neutrophiles. Physical examination showed practically nothing except the facies of extreme pain and near-collapse, profuse sweating and visible and palpable sclerotic superficial vessels. His lungs were clear at this time in front, and apparently clear in the back so far as could be ascertained from slipping the diaphragm of a stethoscope under his back. He seemed too ill to justify turning him over or raising him in bed. A surgeon examined him and agreed that no condition requiring operation was present.

At 11:45 p.m. he was sleeping after a second dose of 1/4 grain of morphine and 1/150 grain of atropine. His pulse showed a rate of 88 and was less tense than on admission. A fall in blood pressure was suspected but rest was so imperative that he was not disturbed to take his pressure. His abdomen was soft. Another surgeon looked at him and agreed that he did not have any surgical abdominal condition. The next morning the patient's systolic pressure had dropped 90 mm. Hg. Further examination was postponed because of his need of rest. However, he looked very ill, so that afternoon a cardiologic consultant was called. In addition to the findings already described he noted the following points: The pain was decidedly worse with respiration and was much relieved by holding his breath; there was a definite paradoxical pulse with the inspiratory pressure 15 mm. below the expiratory; the expansion of the left chest was diminished, especially in the upper part and there was prominence of the left chest, especially in its upper portion; there was obliteration of cardiac dullness on the left, because of striking drum-like tympany over the left upper lobe anteriorly, with dullness to the right of the sternum and evident displacement of the heart to the right; there was obliteration of the point of maximum impulse, with systolic pulsation of the entire left chest; flatness and marked dullness were noted to the right of the sternum and tubular breathing in the left base and axilla. A to and fro friction rub synchronous with the heart beat was heard in the suprasternal notch and faintly along the right and left sternal margins. There was also a poorly audible "klunk" heard best in the suprasternal notch and but faintly over the base of the heart.\*

Hemopneumothorax was suspected and coronary occlusion excluded. At this point it was decided to attempt to make some roentgen-ray films of the patient's chest. Now another interesting symptom appeared, viz., that the patient would apparently start to suffocate and have agonizing pain if he turned on his right side, as if something were cutting off his airway, so he was not allowed to do this further.

The roentgenologic report, by Dr. P. W. Flagge, was as follows:

"(1/30/42) Flat anteroposterior and posteroanterior in lateral position. The flat anteroposterior position shows the left side of the chest generally clouded, with the mediastinum pushed far to the right, apparently  $\frac{3}{4}$  inch beyond the right border of the heart. This line runs almost straight up and down the chest on the right side, about  $2\frac{1}{2}$  inches beyond the right margin of the spine. The left lung is generally clouded, though it appears collapsed. The free cavity is filled with some opaque fluid which leaves the impression of the shadow of blood, because of the irregularity of the density. The diaphragm is pushed far down. The 'lat.' (posteroanterior with patient lying on left side) film shows nothing except a cloud on the left side with the mediastinum shifted back toward the left side, close to the margin of the spine. The right lung appears to be normal."

\* This hitherto undescribed aortic friction rub was discovered by the cardiologic consultant, Dr. Tinsley R. Harrison, and we suggest that it be known in the future as "Harrison's sign." The "klunk" presumably was the sign described by Skerrett.<sup>40</sup>

At two o'clock the following morning, the patient's nurse reported that he had coughed, and was immediately seized with an agonizing pain along the course of the left clavicle. A competent nurse of long experience, she described it as about the worst pain she had ever seen a patient have. Then his pupils dilated and he appeared to be dying. Additional morphine was ordered. Soon he revived somewhat and was suffering less. A few minutes later he made an effort to sit up, as if to breathe better, and again developed extreme pain along the left clavicle and struggled hard to get his breath. He then turned on his left side and became more comfortable.

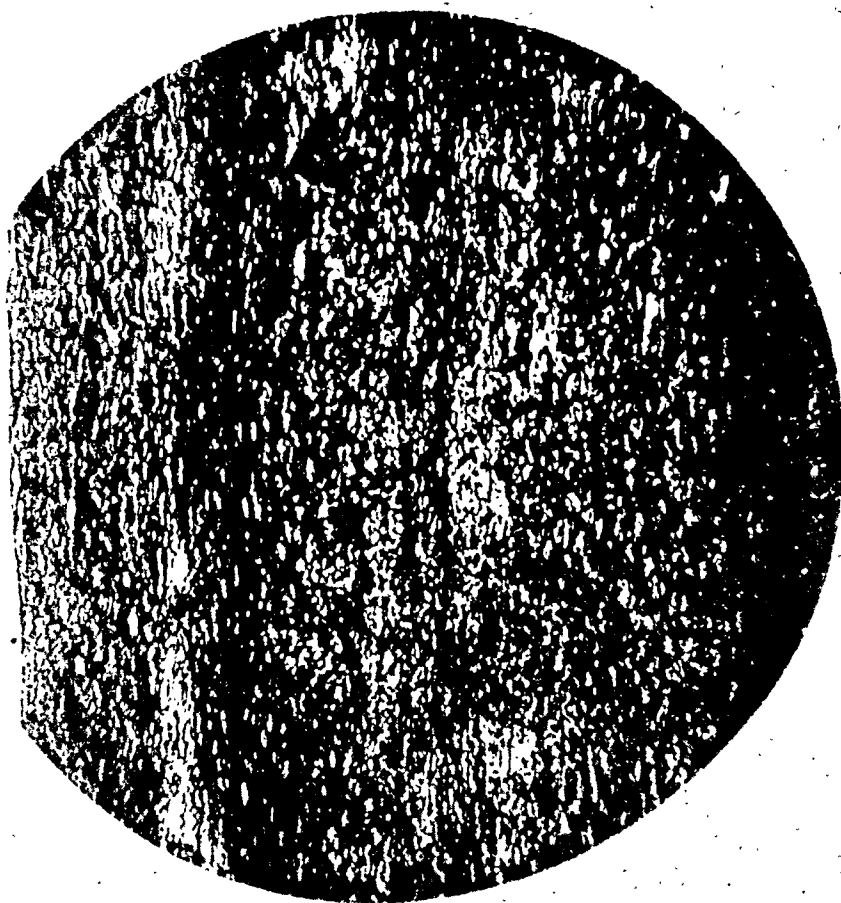


FIG. 1. Fragmentation of the elastic lamellae with the formation of vacuolated spaces. Note that the intima as well as the entire thickness of the media is involved. Weigert's elastic fiber stain.

A consultant in chest diseases, Dr. M. D. Bonner, was called at this time. His physical findings were much the same as Dr. Harrison's. He made three diagnostic punctures in the anterior part of the left chest. Two of these were made in the second interspace over the area of greatest tympany, in an attempt to measure any positive air pressure with a pneumothorax apparatus. The third puncture was made in the anterior axillary line in the area where tubular breathing was most marked. The puncture in the second interspace nearest to the midline (about  $1\frac{1}{2}$  inches from the left edge of the sternum) yielded neither blood nor air. The other two punctures yielded pure blood. The patient continued to get worse, so at 1 p.m. Dr. Bonner

aspirated between 400 and 500 c.c. of blood from the left chest. He got no air on this aspiration, either, despite the persistent tympany. The patient became progressively worse and died about 2:30 the next morning.

*Necropsy Report.* The body was that of a well-developed and well-nourished adult male. A tumefaction was present on the left side of the neck just above the clavicle which measured approximately 8 cm. in diameter and was elevated about 4 cm. above the surface. The external examination was otherwise not remarkable.

When the sternum was removed the pericardial connective tissue was found to

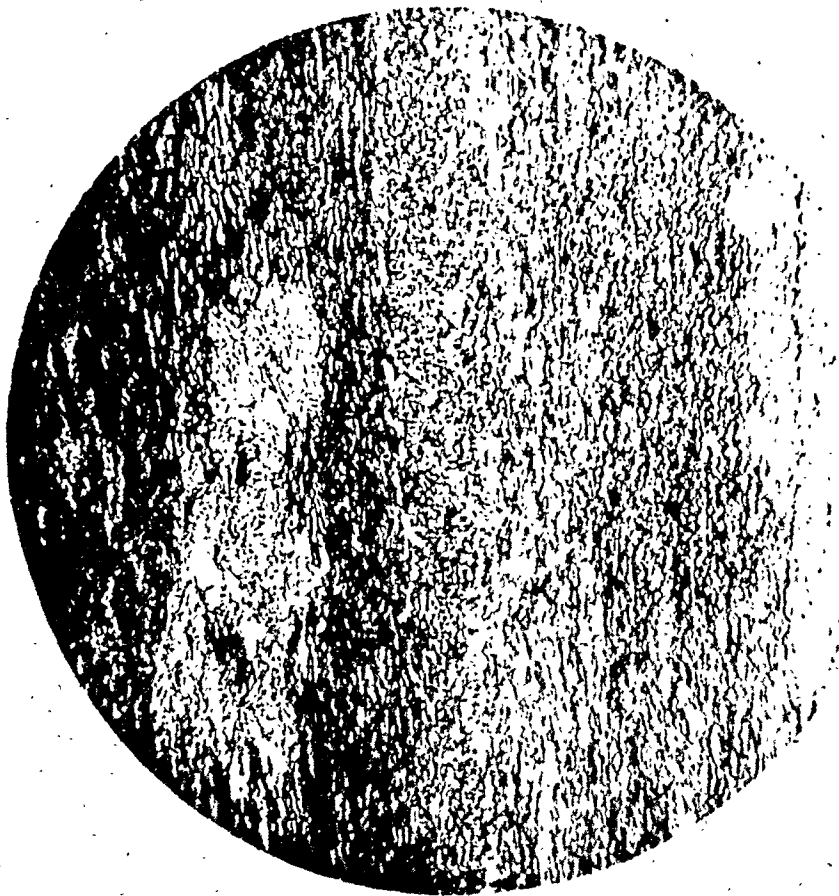


FIG. 2. "Medionecrosis aortae idiopathica cystica." The inner layer of the media shows marked degeneration with almost complete disappearance of elastic tissue. Weigert's elastic fiber stain.

be diffusely infiltrated with brownish black blood. This infiltrative process continued on either side of the pericardial sac, and in the hilar region of each lung dissected for a short distance beneath the pleura. Superiorly, the dissection continued to involve the loose tissue surrounding the aorta and extended upward to produce the tumefaction in the neck. Inferiorly, the same type of clot was seen to surround the aorta to the point of origin of the renal arteries.

The pericardial sac was incised and the epicardium and pericardium were found to be everywhere smooth and glistening, with no evidence of free blood.

The heart weighed 450 gm. and was without evident valvular lesion. At its



widest point the left ventricle measured 2.5 cm., and the right 0.8 cm. in thickness. A diffuse sclerotic process was noted in the coronary radicles and in several instances atheromatous plaques encroached to a considerable degree upon the coronary lumina.

Aortic atherosclerosis was of moderate degree and classical in distribution. There was no evidence of stellate or longitudinal wrinkling, nor were the vessels thickened or indurated. At a point 9 cm. from the aortic ring a transverse tear involving one-third of the circumference of the vessel was noted. Extending upward in an oblique direction and continuous with the first-described tear was a second vascular

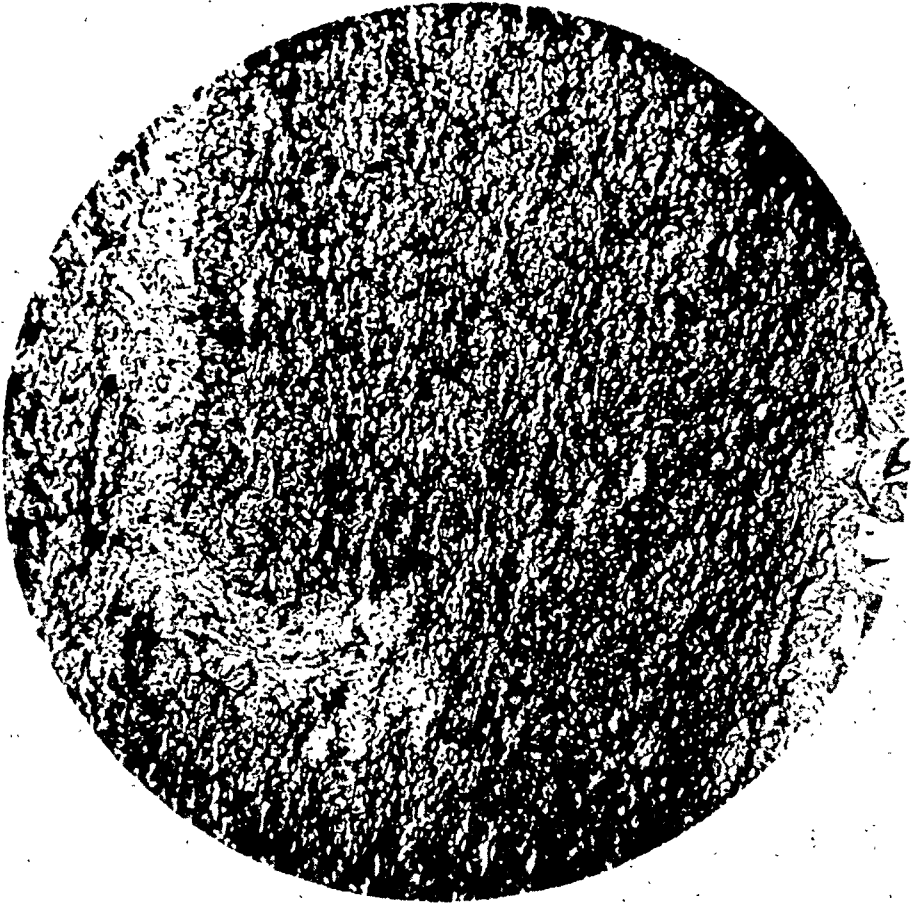


FIG. 3. Incomplete rupture of the aorta with healing. A well defined scar unites the outer half of the media. Weigert's elastic fiber stain.

rent which involved two-thirds of the circumference. The entire thickness of the wall appeared to be involved. The torn edges were 0.8 cm. distant from each other at the widest point and the tear gradually tapered toward the ends. Brownish black clot formed the base of this crater and infiltrated in all directions therefrom.

The right pleural space contained about 750 c.c. of blood and blood clot, and a small amount of blood was noted in the left pleural space. The lower lobe of the left lung was completely atelectatic, as was the posterior three-fourths of the upper lobe. The anterior one-fourth of the upper lobe was crepitant and emphysematous.

The microscopic findings of interest were confined for the most part to the vascular system. Atheromatous plaques were numerous and advanced in the cor-

onaries, but the myocardium did not show significant degenerative or fibrotic changes.

Microscopic examination of the aortic intima revealed changes more extensive than were suspected in the gross examination. Sections stained with Scharlach R showed large lipoid deposits throughout the wall and a thickened fatty intima. Sclerosis was prominent, while in many areas young vascularized connective tissue and areas of myxomatous degeneration were seen. Atherosclerotic plaques were fairly numerous and in each instance medial atrophy was noted opposite the plaques.



FIG. 4. Intima at the point of rupture. Masson's trichrome stain.

Intimal thickening and fatty deposits were most marked in the immediate vicinity of the rupture.

Medial changes were present throughout the aorta and consisted for the most part of distortion and fragmentation of elastic lamellae (figure 1). Necrosis was both diffuse and localized, and in sections stained with hematoxylin and eosin, acellular areas filled with homogeneous basophilic material, with and without cyst formation, were present (figure 2). This picture is similar to that described by Erdheim<sup>14</sup> and others and called by them "Medionecrosis aortae idiopathica cystica." All layers of the media appeared to be affected equally with no predilection for the outer third; however, the degenerative changes were most marked in the region of rupture and

opposite the atherosclerotic plaques. In several instances medial scars were seen, with fibroblastic proliferation (figure 3).

The vasa vasorum of the adventitia were particularly interesting, in that they showed moderate arteriosclerosis throughout the extent of the aorta, while in the immediate vicinity of rupture the process was marked, with complete lumen obliteration, thrombosis and even recanalization.

The picture in the region of rupture was that of tearing without dissection (figures 4 and 5). In several instances, sections through the point of rupture included atherosclerotic plaques, but in no instance did the line of rupture course through one of these plaques.



FIG. 5. Media at the point of rupture. There is no evidence of dissection. Areas of cystic degeneration are seen in the line of rupture. Weigert's elastic fiber stain.

#### PATHOLOGICAL COMMENT

From the above findings one can reason logically as to the histogenesis of rupture in this case. Degeneration of the outer portion of the media was in all probability due to ischemia, the result of adventitial arteriosclerosis. Middle and inner medial degeneration appeared to be secondary to atherosclerosis and injury to the vasa vasorum. The latter finding may be ex-

plained on the basis of increased intra-aortic pressure, as has been pointed out by Dill and Isenhour.<sup>12</sup> The presence of scars and evidences of repair suggested that the process had been of some duration. It is difficult to explain why the intimate vasculature of the aorta should be more involved at one point than at others, but this is a well-known feature of the disease and occurs in other organs. It is natural that rupture should occur in the area in which ischemia was most pronounced.

We do not propose that this mechanism is responsible for all cases of spontaneous rupture of the aorta. In many cases, especially in the young, one obviously must seek other etiologic factors. In some a necrotizing toxin has been frequently indicated, while in others infection cannot be eliminated.

It has been shown that healed medial scars are a not infrequent finding in routine examinations of the aorta. These may be the result of the healing of lesions which have the same etiologic basis as those which go on to rupture in other cases.

As Klotz and Simpson have suggested,<sup>24</sup> cases of spontaneous rupture of the aorta should be divided into two groups, those occurring in patients under 40, and those in patients above that age. In the younger group, the medial necrosis is of unknown etiology, but has been suspected to be of toxic or infectious nature. In the older group we are of the opinion that in most instances careful study will reveal degenerative vascular disease as the basis of the aortic lesions. We feel that in both groups the fundamental pathologic changes in the aorta are identical.

#### CLINICAL COMMENT \*

At its onset this case was considered to be one of coronary occlusion. The rapid development of signs of fluid in the chest, however, excluded that condition and pointed to hemothorax. The tympanitic areas described strongly suggested the presence of air, in addition to the blood, in the pleural cavity. The roentgenologic findings and the results of needling, however, although positively establishing the existence of hemothorax, gave no evidence whatever of pneumothorax, and Dr. Bonner finally concluded that the tympany might be explained by compensatory emphysema of portions of the lung not collapsed by the hemothorax. In the light of the necropsy findings we now regard the increase of pain and the suffocative attacks in certain postures as due to pressure from blood clots on certain nerves and on the trachea. The pathogenesis of the peculiar sounds synchronous with the heart beat heard in the suprasternal notch seems worthy of special consideration. The "klunk," we believe, was made by the leakage of blood, and the friction sound we attribute to friction of the aorta against fibrin in the blood clots surrounding and pressing against it.

\* Some months after the patient's death this case was discussed at a clinico-pathologic conference by Dr. Arthur Grollman, who made a definite clinical diagnosis of rupture of the aorta before the necropsy findings were revealed to him.

## ETIOLOGY

This is obscure in the cases under discussion, i.e., those in which little or no gross change can be seen at the point of rupture. In some cases hypertension appears to be a predisposing cause, in others it is absent. Cases following minor trauma, effort or strong emotion may well be included in our group, and in such cases those factors may or may not be precipitating causes. Rupture of the aorta is more frequent in males, and in middle or later life, though a considerable number of cases have been reported in youth, and a very few in childhood. The age limits of cases collected from the literature by Achard and Paiseau<sup>1</sup> were 13 and 87 years. A number of cases have occurred during labor, as has already been noted. Kountz and Hempelmann,<sup>25</sup> and also Klotz and Simpson,<sup>24</sup> have reported cases following thyroidectomy in hypertensive patients.

## PATHOLOGY

As Klotz and Simpson<sup>24</sup> point out, the storm center in discussions of the pathology of aortic rupture, with or without dissecting aneurysm, has been the question of whether such rupture can occur in an aorta with a perfectly healthy wall. Many have argued a priori that this is impossible. Others argued a posteriori that many ruptures had actually occurred in which skilled, even eminent pathologists could find no evidence of disease. However, in 1928 Gsell<sup>19</sup> attributed rupture to medial necrosis. In 1929, Erdheim<sup>14</sup> described a process, hitherto unrecognized, which he called *medionecrosis aortae idiopathica*, and in 1931 Cellina added a hitherto unknown form which he called *medionecrosis aortae disseminata*, an unusually diffuse form of necrosis of the media. In 1932, Moritz<sup>31</sup> confirmed Erdheim's findings, as have several others since.

Moritz describes *medionecrosis aortae idiopathica cystica* as a condition in which there is an increase in homogeneous, pale-staining, basophilic, acellular material in the media between the muscle cells and elastic fibrils. This may be found throughout the aorta, but is especially likely to be noted in the ascending arch. It is stained red with thionin, and light red or rose with cresyl violet R or polychrome methylene blue. It shows a distinct affinity for fat, and in one case showed an affinity for calcium. This condition was seen in slightly less than 10 per cent of adult aortas, but it was more marked in the three cases of rupture described by them. As these lesions progressed, they became cystic, and the chromatotropic substance lost its specific staining properties and became serous. Fat droplets, present in the early lesions, were absent in the cysts.

The essential underlying pathology, excluding factors such as atheroma, syphilis, major trauma and the various other conditions noted in our classification, appears to be the same, with or without the formation of a dissecting aneurysm, except for the element of time. If the rupture is sufficiently

gradual, a dissecting aneurysm forms; if not, it does not form. Many, perhaps most, authorities now believe that some form of medial necrosis, either Erdheim's or Cellina's type, is a prerequisite for "spontaneous" rupture as it is defined here. Cellina's type appears to be unique, but many observers, as stated above, have confirmed Erdheim's findings.

Grossly, the ruptures vary in size, location, form, direction and number. The size may vary from a mere puncture point to a tear several centimeters long. The location may be anywhere in the aorta, thorax or abdomen, but it is most frequent at or near the origin of the thoracic aorta and decreases in incidence distally. The form is usually a gaping slit, which may be clean-cut or irregular. Occasionally, however, a more or less circular hole is encountered. The direction of the rupture, when slit-like, may be longitudinal, transverse or oblique, some oblique ruptures involving the entire circumference of the aorta in a spiral. So far as number is concerned, a single rupture is the rule, but two or even three ruptures have been described. Multiple ruptures usually have been confined to the thoracic aorta, but in Brouardel and Vibert's case, already cited,<sup>7</sup> there was one rupture in the thoracic aorta and another in the abdominal. This case, it will be recalled, was the unique one with the paper-like thinness of the aortic wall.

When the rupture is intrapericardial, cardiac tamponade occurs. When it is extrapericardial, in the thorax, the blood may go into the mediastinal spaces and pleural cavities, and spread widely throughout the chest. In some cases in which the patient has survived several days, actual signs of healing of the initial stages of the rupture have been noted, and Ernst,<sup>15</sup> Fränkel,<sup>16</sup> Beneke,<sup>4</sup> and Schmorl<sup>38</sup> have reported complete healing of aortic rupture. Rupture into the pericardium is the most frequent type of rupture; Achard and Paisseau collected 66 cases (usually with dissecting aneurysm) of intrapericardial rupture, but only 19 cases of rupture into one or both of the pleural cavities. Rupture into the stomach with hematemesis, into the bronchi with hemoptysis, or into the peritoneal cavity is a rare event, and in the first two instances of these is usually associated with some extrinsic factor such as aortic syphilis, malignant invasion, etc. When death is practically instantaneous, it is probably due to ventricular standstill or fibrillation brought about by the shock of the rupture. In all other cases, if the rupture is intrapericardial, death is due to cardiac tamponade; if extrapericardial, to the massive hemorrhage.

Rupture into the left pleural cavity appears to be much commoner than rupture into the right; in Achard and Paisseau's series there were 16 cases of rupture into the left, two into the right, and one into both. This preponderance of rupture into the left side seems to be due to the fact that the aorta descends to the left of the spine. When rupture occurs in the ascending aorta, to the right of the spine, it is usually intrapericardial, and goes into neither pleural cavity. Enormous amounts of blood may be lost into a pleural cavity, such figures as 1420 c.c. (Achard and Paisseau<sup>1</sup>), 1700 c.c.

(Thoinot and Bernard <sup>41</sup>), 1800 c.c. (Brouardel and Vibert <sup>7</sup>), about 2000 c.c. (Gougerot <sup>18</sup>), and even the extreme figure of 3500 c.c. (DeAngelis <sup>2</sup>), appearing in the literature. In intrapericardial rupture, the limitation of the space plus the fatal effects of cardiac tamponade prevents such enormous losses, though Achard and Paisseau collected from the literature some remarkable figures, such as 640 c.c., 700 c.c., 800 c.c., 1000 c.c., and even 1500 c.c.

### SYMPTOMATOLOGY AND DIAGNOSIS

The symptoms occurring in spontaneous rupture of the aorta are of two main types. In the first type there is merely a terrific pain in the chest, back or abdomen; the patient gives a few gasps or convulsive movements and dies in a few moments. Clinical diagnosis is impossible in such a case. In the second type, the patient survives long enough to permit of physical examination, and often certain other procedures, such as roentgenologic study, that may lead to a tentative diagnosis, at least. It is often impossible to determine whether or not a dissecting aneurysm is present, though mathematical probability greatly favors its presence. If there is a history of two separate attacks of pain, the longer the interval between the two, the greater is the likelihood of a dissecting aneurysm's being present; but this rule is by no means infallible. Sometimes after the first pain due to intimal rupture, there will be more or less constant pain due to the dissecting process, with a final exacerbation of pain due to adventitial rupture and infiltration of the fibrous mediastinal tissue, if the rupture is extrapericardial. Extensive progressive spread of the area of pain, especially when it reaches high up in the neck or down into the abdomen, strongly suggests dissecting aneurysm, though the absence of such spread does not exclude it.

In patients surviving long enough, a train of symptoms develops which should suggest, sooner or later, the rupture of a large blood vessel, when the rupture occurs in the thorax. If the abdominal aorta is ruptured, the condition may be impossible to differentiate from rupture of some intra-abdominal viscus. As rupture of the abdominal aorta, apart from major trauma or syphilitic aneurysm, is exceedingly rare, we shall confine our remarks to intrathoracic rupture.

Most of the case reports prior to the present century describe a single prolonged episode of pain, whereas the more recent reports describe more cases showing two definite attacks of pain, separated by an interval in which symptoms are more or less in abeyance. We shall describe the latter type of clinical picture, as the former differs from it in no way save in the absence of the preliminary pain.

As Kaufmann <sup>23</sup> points out, rupture of the aorta is often a slow process. A small fissure may develop in the intima, due, perhaps, to some sudden increase in intravascular pressure, or merely to a giving way in the face of normal pressure, but the tearing of the other coats may proceed so gradually that no violent symptoms result until the adventitia gives way.

Discussing the duration of survival, Achard and Paisseau cite a large number of cases from the literature in which death occurred anywhere from a few seconds to eight days after the initial attack. As most of these were cases of dissecting aneurysm, however, we can hardly utilize them as the basis for conclusions as to the duration of life after the onset of a spontaneous rupture without such aneurysm. We can hardly be more definite on this point than to say that the patient may survive from a few seconds to a few days. It is natural to ask how anyone can survive more than a few seconds after rupture of the main arterial trunk of the body. There are two reasons for this survival: (1) the fact that, even without the formation of a dissecting aneurysm, the rupture may occur in stages; and (2) the fact that, in many instances, even after the adventitia ruptures, the rupture is so located that the blood can escape only into dense resistant mediastinal fibrous tissue or into the pericardial or pleural cavities, which quickly develop a positive pressure that decreases the rapidity of the blood loss.

The location of the pain is varied. In cases in which the rupture is into the pleural cavity the pain has been reported as thoracic, anginoid, in the side, in the back, in the abdomen, in the epigastrium, in the chin or jaw, etc. The pain appears to be due, not only to the rupture itself, but also to infiltration of blood into the dense cellular connective tissue around the aorta, to irritation of the pleura, etc. Abdominal pain may be due to irritation of the diaphragmatic pleura or occasionally to infiltration of blood along the aorta through the diaphragm down to the celiac area. Rupture into the pericardium may cause precordial, substernal or epigastric pain.

(Rupture of the abdominal aorta may show as its chief symptom severe intermittent pain in a testicle, as in Nicory's case<sup>34</sup> in which this symptom appeared at onset on the right side, cleared up during the night and recurred the next day, when the patient died. In other cases the pain may be intra-abdominal.)

Dyspnea may or may not accompany the initial pain, but as a rule it does not. Occasionally, as in Rose's patient,<sup>37</sup> it, rather than pain, may be the presenting initial symptom. It practically always occurs sooner or later, due to cardiac tamponade or massive hemorrhage.

The temperature may be normal, subnormal or elevated at onset, but it almost always rises to a moderate fever in patients that survive many hours. The pulse is usually rapid, but may be slow. An increase in the number of neutrophilic leukocytes usually develops very rapidly and reaches a high level, often 20,000 or more, within the first hours after the onset of symptoms, in contrast to the slowly developing and moderate leukocytosis found in association with coronary thrombosis.

Skerrett<sup>40</sup> described a unique physical sign in a case of rupture. His patient, a 71 year old man, collapsed while sitting on a water-closet. He was pale, unconscious and cyanotic, with no perceptible pulse. He took only short breaths at intervals. His heart sounds were feeble, but "also over the precordium there was a continuous adventitious sound which may be de-



scribed as gurgling or lapping, as of a cat lapping milk. This altered in character, the successive laps becoming more rapid and finally lost." It was totally independent of the heart sounds and quite different from any other sound Skerrett had ever heard in the chest, and suggested at once the leakage of blood. Skerrett thought that the heart muscle had ruptured but necropsy showed that a dissecting aneurysm had ruptured into the pericardium.

To sum up, the cardinal symptoms of spontaneous rupture of the aorta are intense pain, usually thoracic, anteriorly or posteriorly, sometimes abdominal; dyspnea; collapse; and evidence of either cardiac tamponade or of the rapid accumulation of blood elsewhere in the thoracic cavity, or in the abdomen, if the abdominal aorta is ruptured. Often this picture is preceded for hours or days by an initial pain which may be slight or severe, but which usually subsides in part, at least, to be followed by the final major symptoms.

There is no special pattern to the pain. Its varied location has already been mentioned. Its intensity may vary from slight to agonizing, except in the final adventitial rupture, when it is of almost unique intensity.

Most of these cases are erroneously diagnosed as coronary occlusion at their onset, as was our case. The rapid accumulation of fluid in the chest, when the rupture is extrapericardial, will reveal this error in time. In intrapericardial cases the diagnosis is more difficult; for even when two separate pains occur, the first one may resemble an ordinary anginal attack very closely. When leakage into the pericardium is slow, a paradoxical pulse is likely to develop. When either Harrison's or Skerrett's sign is present, a correct diagnosis may be possible. The high leukocyte count developing within a few hours after adventitial rupture is against coronary occlusion. As has already been mentioned, a progressive extension of the pain, especially into the lower abdomen or upper neck, is strongly indicative of a dissecting aneurysm with impending rupture of the aorta and the occurrence of intermittent signs of aortic insufficiency is also highly suggestive of the condition. The absence of these findings, however, does not invalidate the diagnosis. Normal electrocardiographic findings or evidence of simple left axis deviation are to be expected in aortic rupture with or without dissecting aneurysm. When hemothorax causes marked cardiac displacement the electrical axis may shift accordingly. Respiration does not increase the pain of coronary occlusion.

#### TREATMENT

This can only be directed towards relieving the agonizing pain of what is inevitably the patient's final illness, and consists of large and frequently repeated doses of morphine or some similar drug, as needed.

#### SUMMARY

1. Rupture of the aorta is by no means infrequent in the anatomical, as well as the pathological and clinical literature.

2. It occurs without the formation of a dissecting aneurysm more often than is usually realized, though the cases with dissecting aneurysm are much more numerous.

3. The literature on the type of rupture occurring without dissecting aneurysm has been reviewed and an additional case of our own presented, with clinical and pathological findings.

4. The gross and microscopic pathology of the condition is discussed.

5. Certain diagnostic criteria, including a hitherto undescribed physical sign, have been suggested.

6. The prognosis is hopeless and treatment is purely symptomatic.

#### BIBLIOGRAPHY

1. ACHARD, C., and PAISSEAU, G.: Rupture de l'aorte, *Presse méd.*, 1905, i, 177.
2. DEANGELIS, F.: Rupture de l'aorte descendante par suite d'une chute peu élevée, *Arch. gén. de méd.*, 1836, II<sup>e</sup> Serie, x, 222.
3. BALTZAN, C. M.: Diagnosis of some major vascular accidents, *Canad. Med. Assoc. Jr.*, 1938, xxxviii, 45.
4. BENEKE: Discussion of Ernst's paper, loc. cit.
5. BOHNEN, P.: Über einen Fall von Aortenruptur unter der Geburt, und einen Fall von 'Septumdefekt', *Zentralbl. f. Gynäk.*, 1927, li, 2398.
6. BRIGHT, R.: Rupture spontanée de l'aorte. Thèse présentée et publiquement soutenue à la Faculté de médecine de Montpellier, le 1<sup>er</sup> avril, 1908, pour obtenir le grade de Docteur en Médecine. Montpellier, Imprimerie coopérative ouvrière, 1908.
7. BROUARDEL, P., and VIBERT, C.: Rupture de l'aorte thoracique chez un jeune homme de vingt ans, *Ann. d'hyg. pub.*, Paris, 1892, 3<sup>e</sup> s., xxvii, 451.
8. BROWNING, B.: Rupture of aorta within pericardium, *Brit. Med. Jr.*, 1871, ii, 661.
9. CELLINA, M.: Medionecrosis disseminata aortae, *Virchow's Arch. f. path. Anat.*, 1931, cclxxx, 65.
10. CIVEL, and LENOBLE: Mort subite par rupture spontanée de l'aorte athéromateuse chez un sujet atteint de fracture de jambe, *Bull. et mém. Soc. anat. de Paris*, 1899, lxxxiv, 90.
11. DARCANNE, THIERCELIN, and BENSAUDE: Rupture spontanée de l'aorte. Aorte non-athéromateuse, *Bull. et mém. Soc. anat. de Paris*, 1900, 6 s., ii, 975.
12. DILL, L. V., and ISENHOUR, C. E.: Occurrence of atheroma in rabbits with renal hypertension, *Arch. Path.*, 1942, xxxiii, 655.
13. DRAPER, G. A.: Rupture of aorta, *Jr. Roy. Army Med. Corps*, 1904, ii, 164.
14. ERDHEIM, J.: Medionecrosis aortae idiopathica, *Virchow's Arch. f. path. Anat.*, 1929, cclxxiii, 187.
15. ERNST, P.: Geheilte zirkuläre Aortenruptur am Isthmus, *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1904, xv, 548.
16. FRÄNKEL: Discussion of Ernst's paper, loc. cit.
17. GARDETTE, M. L. H. A.: Des ruptures spontanées de l'aorte dans le péricarde, 1891, Bordeaux, p. 40.
18. GOUGEROT: Mort subite par rupture de l'aorte athéromateuse non ectasiée, *Bull. et mém. Soc. anat. de Paris*, 1904, lxxix, 562.
19. GSELL, O.: Wandnekrosen der Aorta als selbständige Erkrankung und ihre Beziehung zur Spontanruptur, *Virchow's Arch. f. path. Anat.*, 1928, cclxx, 1.
20. HALBRON, P.: Rupture de l'aorte, *Bull. et mém. Soc. anat. de Paris*, 1904, lxxix, 372.
21. HAMMAN, L., and APPERLY, F. L.: Clinical pathologic conference; instance of spontaneous rupture of aorta with aortic insufficiency, *Internat. Clin.*, 1933, iv, 251.

22. KACZANDER, P.: Über Aortenrupturen, *Ztschr. f. Kreislaufforsch.*, 1928, xx, 665.
23. KAUFMANN, O. J.: A case of rupture of the thoracic aorta, *Lancet*, 1901, i, 401.
24. KLOTZ, O., and SIMPSON, W.: Spontaneous rupture of the aorta, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 455.
25. KOUNTZ, W. B., and HEMPELMANN, L. H.: Chromatotrophic degeneration and rupture of aorta following thyroidectomy in cases of hypertension, *Am. Heart Jr.*, 1940, xx, 599.
26. LETULLE, M.: Rupture spontanée de l'aorte, *Presse méd.*, 1907, xv, 847.
27. LEVINSON, B.: Über tödliche Aortenzerreissung aus geringen Ursachen, *Virchow's Arch. f. path. Anat.*, 1931, cclxxii, 1.
28. MACKINNON, D. A.: Rupture of the thoracic aorta, *Brit. Med. Jr.*, 1939, ii, 114.
29. MARTIN-DURR: Mort subite par rupture spontanée de l'aorte, *Bull. et mém. Soc. anat. de Paris*, 1891, 5<sup>e</sup> s., v, 38.
30. MORGAGNI, J. B.: De sedibus et causis morborum, epist. XXVI, arts. 7, 15; epist. XXVII, art. 28; epist. LIII, art. 34; English translation by BENJAMIN ALEXANDER, dedicated to Dr. Fothergill, London, 1769.
31. MORITZ, A. R.: Medionecrosis aortae idiopathica cystica, *Am. Jr. Path.*, 1932, viii, 717.
32. NARR, F. C., and WELLS, A. H.: Rupture of aorta, *Am. Heart Jr.*, 1933, clxxv, 115.
33. NEUBÜRGER, K.: Aortenveränderungen bei Spontanruptur, besonders über die mukoid-cystische Entartung der Aortenmedia, *Ztschr. f. Kreislaufforsch.*, 1932, xxiv, 169.
34. NICORY, C.: Rupture of abdominal aorta; death from acute intestinal obstruction, *Brit. Med. Jr.*, 1923, ii, 413.
35. NORRIS, J. C.: Rupture of aorta contrasted with rupture of aortic valve cusp, *South. Med. Jr.*, 1939, xxxii, 475.
36. ROCHARD, and DEBELLY: Rupture spontanée de l'aorte abdominale au début d'une laparotomie, *Bull. et mém. Soc. anat. de Paris*, 1909, lxxxiv, 564.
37. ROSE, T.: Rupture de l'aorte sans anévrisme, *Arch. gén. de méd.*, 1828, xvi, 263.
38. SCHMORL, G.: Geheilte Aortenruptur, *München. med. Wchnschr.*, 1914, lxi, 791.
39. SIBLEY: Rupture of the aorta, *Trans. Path. Soc. Lond.*, 1864, xv, 74.
40. SKERRETT, F. B.: Rupture of dilated aorta; leakage bruit, *Brit. Med. Jr.*, 1907, i, 435.
41. THOINOT, and BERNARD, H.: Note sur la rupture de l'aorte avec détermination d'hématome souspleurale, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1897, 3 s., xiv, 1178.
42. DEVRIES, W. M.: Over Oartanruptuur, *Nederl. Tijdschr. v. Geneesk.*, 1922, ii, 2713; *abst. Jr. Am. Med. Assoc.*, 1923, lxxx, 1112.

# AN EVALUATION OF THE DARK TEST\*

By PAUL H. WOSIKA, M.D., M.S., PH.D., *Chicago, Illinois*

## INTRODUCTION

OVER 40 methods and apparatus have been described in the past 85 years, claiming to measure the time necessary for the eye to become accustomed to low illumination (scotopic vision). Delayed dark adaptation (dysaptation) has come to be considered minimal or subclinical night blindness (hemeralopia). Of academic interest at first, the changes in the manner of living and lighting in this century have produced new demands upon adaptation ability and new interest in this phenomenon. Then, too, new impetus for study appeared following the claims that lack of vitamin A was the specific deficiency of night blindness, xerosis and xerophthalmia (Pillat, 1929-1940; Tassman, 1932). As a result of these and other studies it was assumed that the lack of vitamin A was responsible for poor dark adaptation.

Reports of dark adaptometry have been numerous (Wosika, 1943). Many workers have stated that large blocks of the population showed poor dark adaptation. Further, their results have shown that the administration of vitamin A improved this vision at low luminosity and on this basis have recommended, enthusiastically, massive doses of vitamin concentrates for all people. Other workers, although dubious of existing methods, have agreed in principle and have offered modifications or new apparatus for the dark test. Still others have found no relationship between dysaptation and vitamin A.

The present work was undertaken to establish, if possible, the reliability of the Bio-photometer. There can be no question that the machine measures the perception of dim light. This it has in common with all adaptometers. However, when the attempt is made to translate the results into a chemico-physiologic process concerning vitamin A, great difficulty is encountered.

The present war emergency would seem to make this report timely. Practically, it would be of great importance to be able to find and correct delayed visual adaptation to low illuminations, particularly since the occurrence of dimouts and blackouts. Theoretically, a certain percentage of accidents in the air and on the highway might thereby be eliminated.

## PROCEDURES

For this study 700 ambulatory patients were taken at random from the clinics of Northwestern University Medical School. Patients found with poor dark adaptation were examined by ophthalmologists and rejected if local disease of the eye was disclosed. Conditions such as retinitis pigmentosa were not included in the series.

\* Received for publication April 30, 1943.

The patients were between 15 and 78 years of age, the average being 45.5 years. There were almost twice as many women as men. Members of the colored race numbered 84; their average age was slightly over 39, whereas the whites averaged over 46 years.

Medical students, young physicians and various workers from the clinic personnel (80) were used as controls. They constituted a superior group from the economic and intellectual standpoints. They were all of the white race, averaging 26 years, and were without obvious defects.

The instrument used was the Bio-photometer which consisted essentially of a metal box in which a constant source of strong light as well as a much weaker light emanated. The intensity of the weaker light was controlled by a rheostat with the resistance calibrated in millifoot candles. Between the eyepiece and these lights there was interposed a metal screen perforated in the form of a quincunx. The greater resistance to light through these perforations was from right to left. When the rheostat was turned to the right (clockwise) the spots faded. When turned left until the central spot appeared the end point was reached and this point was recorded. The whole screen could be lowered so that the bright source of light reached the eyes unimpeded and was used to exhaust the visual purple.

The technic used was similar to the one reported by Jeans, Blanchard and Zentmire (1937). During the test, the subject was questioned as to diet adequacy. Information on foods high in vitamin A, such as milk, eggs, butter, cheese and leafy green vegetables was specifically noted. No attempt was made quantitatively to resolve the number of international units of vitamin A, since no great accuracy was possible except on theoretical grounds. Workers who have had experience in attempting to evaluate diet histories (Elder and Emery, 1937) will readily understand the difficulties of securing truthful complete histories of foods consumed. In addition, it has been shown that the various common foods vary from season to season in their vitamin A content (Dornbush, Peterson and Olson, 1940). Further, far reaching dietary surveys have shown "that diets which meet the average minimum requirements in other respects furnish in the neighborhood of from 3,000 to 6,000 international units of vitamin A per day to adults." This must be considered adequate when the "minimum requirement" for adults is approximately 2,000 to 2,500 international units per day (Daniel and Munsell, 1937). Therefore, the diets were judged to be sufficient or insufficient, on a qualitative basis. These estimations were made without the knowledge of the dark test results and since one observer made them all, any bias will be equitably reflected throughout the entire series.

## RESULTS

The results of the study are reported in the following tables and graphs.

Table 1 showed for 668 patients the number and percentage of normal, borderline and abnormal Bio-photometer readings occurring with normal (10

TABLE I

The number and percentage of normal, borderline, and abnormal Bio-photometer readings occurring with normal and deficient diets on 668 patients. (Compare with the control series in table 3.)

Bio-photometer Readings	Type of Diet			
	Normal (10%)		Deficient (90%)	
	Number	Per cent	Number	Per cent
Normal	14	20	94	16
Borderline	17	24	138	23
Abnormal	39	56	366	61
Totals	70	100	598	100

per cent) and deficient (90 per cent) diets. Of those considered on suitable intakes 20 per cent of 70 patients were normal, while 16 per cent of 598 patients were normal when the dietary intake was inadequate. Table 2 showed the same data rearranged into a four-fold table. Here the observed frequencies were very close to the expected frequencies. Since the chi-square

TABLE II

Four-fold table of 668 patients showing observed and theoretical (in small box in upper corner of each cell) frequencies of normal and abnormal Bio-photometer readings with normal and deficient diets. Chi-square = 0.84.

	Bio-photometer Readings				Totals
	Normal		Borderline and Abnormal		
Normal Diet*	11.4		58.6		70.0
	14.0		56.0		
Deficient Diet	96.6		501.0		598.0
	94.0		504.0		
Totals	108.0		560.0		668.0

equaled 0.84, the probability equaled about 0.40, which means that about 40 times in 100 chance operates in this association (Pearl, 1940; Davenport and Ekas, 1936).

The results of 80 controls (table 3) showed the number and percentage of normal, borderline and abnormal Bio-photometer readings occurring with normal (30 per cent) and deficient (70 per cent) diets. Of 24 subjects considered to have a normal diet, 79 per cent showed normal Bio-photometer

TABLE III

The number and percentage of normal, borderline and abnormal Bio-photometer readings occurring with normal and deficient diets on 80 controls.

Bio-photometer Readings	Type of Diet			
	Normal (30%)		Deficient (70%)	
	Number	Per cent	Number	Per cent
Normal	19	79	41	73
Borderline	4	17	13	23
Abnormal	1	4	2	4
Totals	24	100	56	100

readings, and 75 per cent of 56 subjects having a deficient diet were normal in adaptometer ability. These data were rearranged into the four-fold table shown in table 4. Here the observed normal Bio-photometer readings were shown and the borderline/abnormal were combined for the sake of simplicity. This first attribute was compared with the presence or absence of a normal diet. The theoretical frequencies were computed on the basis of the prob-

TABLE IV

Four-fold table of 80 control subjects showing observed and theoretical (in small box in upper left corner of each cell) frequencies of normal and abnormal Bio-photometer readings with normal and deficient diets. Chi-square = 0.31.

	Bio-photometer Readings				Totals
	Normal		Borderline and Abnormal		
Normal Diet	18.0		6.0		24.0
	19.0		5.0		
Deficient Diet	42.0		14.0		56.0
	41.0		15.0		
Totals	60.0		20.0		80.0

ability theory and placed in the cells in the small box in the upper left corner. It was noted that in each instance the observed frequencies were almost identical with the theoretical frequencies. This would indicate that the presence or absence of either attribute did not influence the presence or absence of the other. The calculation of the chi-square equaled 0.31 and the probability equaled more than 0.50. Any association existing between

diet and Bio-photometer readings was extremely small since chance operated in more than 50 of 100 instances.

Although men were known to suffer from night blindness with greater frequency than women, the dark test showed no distinction between the sexes. Men showed 18 per cent normal and 82 per cent borderline/abnormal readings. Women showed 16 per cent normal and 84 per cent borderline/abnormal dark test readings. The Bio-photometer readings of men varied slightly

TABLE V

This table compares whites (616 patients) with negroes (84 patients) as regards the Bio-photometer performances.

Bio-photometer Readings	Race			
	White (88%)		Negro (12%)	
	Number	Per cent	Number	Per cent
Normal	92	15	26	31
Borderline	137	22	21	25
Abnormal	387	63	37	44
Totals	616	100	84	100

regardless of diet adequacy. Thus, 21 per cent were normal where the diet was considered sufficient and 17 per cent were normal where the dietary standards were low. Women had a slightly decreased number of normal readings on deficient diets, 13 per cent as against 20 per cent normal readings when the diet was adequate.

Since pigmentation had been considered a factor in the utilization of vitamin A, table 5 was constructed comparing race as regards dark test

TABLE VI

This four-fold table compares the effect of race upon Bio-photometer readings on 700 patients. Chi-square = 13.53.

	Bio-photometer Readings		Totals
	Normal	Borderline and Abnormal	
White	103.8 92.0	512.2 524.0	616.0
Negro	14.2 26.0	69.8 58.0	84.0
Totals	118.0	582.0	700.0



ability. Over twice as many negroes had normal Bio-photometer curves (31 per cent for negroes; 15 per cent for whites). That this increase is real is borne out by table 6. Pigment may be a factor since fewer whites had normal dark adaptation than were expected from the theoretical standpoint. However, almost twice as many negroes had normal dark adaptation as were calculated possible on the basis of a complete independence of these occurrences. Chi-square equaled 13.53 which meant that there was far less than one time in 100 that chance affected negroes' superior dark test ability when compared to whites'.

Several disease processes had been considered to be responsible for poor dark tests. Since there were no diagnosed cases of cirrhosis of the liver or ulcerative colitis among the patients tested, a comparison was made with

TABLE VII

In this table an attempt is made on 679 patients to calculate the effect of blood pressure upon Bio-photometer readings. Chi-square = 24.36.

	Bio-photometer Readings				Totals
	Normal		Borderline and Abnormal		
Low/Normal Blood Pressure	85.2		404.8		490.0
	107.0		383.0		
High Blood Pressure	32.8		156.2		189.0
	11.0		178.0		
Totals	118.0		561.0		679.0

the readily available blood pressure determinations. There was a distinct decrease in the normal readings for the hypertensive group (6 per cent) as compared with the normal (21 per cent). This difference seemed significant. Great discrepancies were found between the actual and calculated values. Although more individuals (among 679) were found to have normal dark tests with normal blood pressure readings than were considered possible theoretically, only one-third of the calculated number was observed in the hypertensive group (table 7). Since chi-square equaled 24.36, there were almost a million and a half chances to one the blood pressure levels somehow influenced the Bio-photometer results.

It is known that the incidence of hypertension increases with age. This is true in the present study.

Figure 1 depicted the spread of normal and borderline/abnormal dark tests throughout the various decades. The great increase in poor adaptometry with advancing years was apparent. Table 8 showed that normal

dark tests occurred more frequently under 40 than were calculated to be possible up to the age of 40. After this time the drop in the number of normal dark tests was great. Chi-square equaled 104.9 which made the association significant (probability equaled less than 0.01).

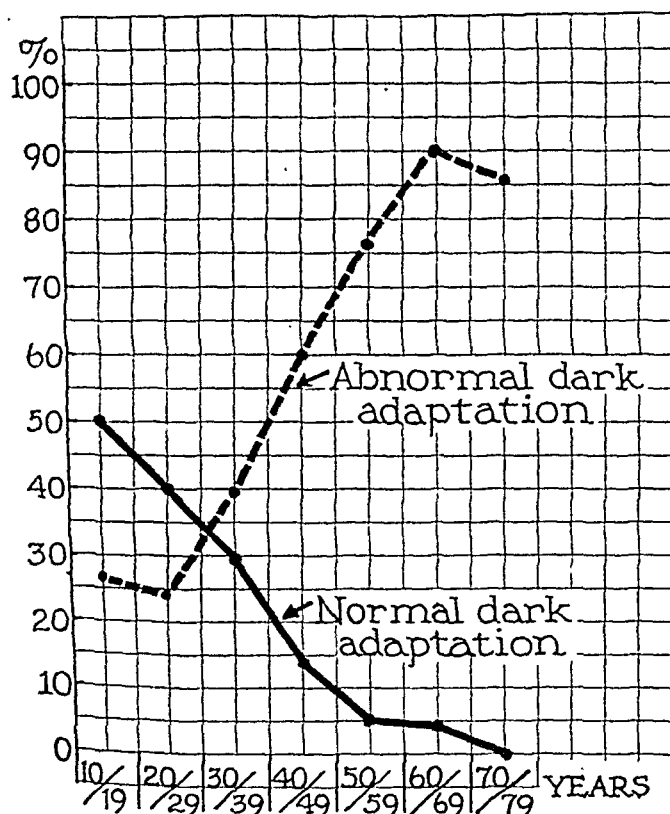


FIG. 1. Graph showing the incidence of normal and abnormal Bio-photometer readings for seven decades on 700 patients.

The possibility of quantitatively and qualitatively decreased diets with increasing age should be considered. In the present series in the advancing years no more deficient diets could be found than among the younger age groups.

### DISCUSSION

The work of Hecht (1920), Fridericia and Holm (1925) and Wald (1935) was of fundamental importance in linking visual purple to light perception and vitamin A, notwithstanding the criticisms of Krause and Sidwell (1936) and Granit et al. (1939). The work of Popper (1940) may serve to strengthen this relationship. Theoretically the dark adaptation test should form a yard stick for the measurement of vitamin A deficiency, although Wessely (1916) cautioned that there was danger in assigning numbers to the dark test.

TABLE VIII

Theoretical (left upper corner of each cell) and observed frequencies of Bio-photometer readings (normal and abnormal) for seven decades. Chi-square = 104.9.

Age in Years	Bio-photometer Readings		Totals
	Normal	Borderline and Abnormal	
10-19	5.7 17	28.3 17	34
20-29	12.3 29	60.7 44	73
30-39	22.0 38	108.0 92	130
40-49	30.0 23	148.0 155	178
50-59	23.8 7	117.2 134	141
60-69	18.0 4	90.0 104	108
70-79	6.0 0	30.0 36	36
Totals	118	582	700

There can be no quarrel with the attempts to discover subclinical vitamin A deficiency. The natural impulse is to accept and to further observations dealing with such a fundamental problem as the nutritional state of the population. The method or methods used are immaterial. The results are important and the therapeutic possibilities of unsuspected insufficiencies challenge all workers for health to coöperative effort. The question at issue, then, is socioeconomic, as well as medical.

The many apparatus designed for resolving visual ability in dim light into figures are all similar, and this fact precludes any claim of specificalness.

Innumerable reports have appeared, hastily confirming the contention of Jeans that vitamin A deficiencies are common. Actually, vitamin A deficiency was certain to be suspected in approximately one-half of the persons subjected to dark adaptation tests since to establish a normal average in any group of persons examined, a certain percentage must be found below as well as above this average.

A series of papers has appeared purporting to show the plausibility of the test on theoretical grounds. These authors devised new machines which they believed were improvements on existing apparatus (Hecht, 1939, Sloan, 1939 and others).

Then, too, other papers have been critical of the value of the test. The reasons are numerous: the lack of correlation of diet, increased or decreased vitamin A intake, blood vitamin A and carotene levels with the dark test values. The training factor, mentality, age and individual differences have been advanced as causative agents of discrepancies in the supposed state of nutrition and mild degrees of night blindness.

The present results are interesting from the standpoint of the large series (780 adults) studied. Comparing the control series with the patients, there would seem to be no doubt that the Bio-photometer reflects a higher percentage of normal readings in the former group. Thus, eliminating for the moment all considerations of the mechanical accuracy of the apparatus, it is seen that for the control series 75 per cent are normal, 21 per cent are borderline and 4 per cent are abnormal, whereas for the 700 patients 17 per cent are normal, 23 per cent are borderline and 60 per cent are abnormal. The conclusion from these figures that the control group is quite superior in the dark test seems to be justified. This has been found to be true in other clinics where similar studies have been made.

Therefore, factors have been sought which might account for this difference. Better food habits according to present standards of dietary intake were considered likely and information upon the present series revealed that for the control group 30 per cent of the individuals were on normal diets, whereas 70 per cent were deficient. The patient series viewed similarly showed only 10 per cent on normal intakes, whereas 90 per cent were on insufficient intakes. If, then, no further analyses are made, it may be assumed that dark adaptation tests are more likely to be normal in control patients whose dietary intake is superior. This has been done repeatedly in the literature.

The present study, however, enabled a more detailed division of the material, and it became apparent at once that when the Bio-photometer readings were considered for the group of controls, 70 per cent and 73 per cent were normal when the diet was normal, or deficient, respectively. The patient series showed 20 per cent and 16 per cent normal readings on normal and deficient diets respectively. Therefore, on the basis of a qualitative examination of food habits, diet alone can not be considered an influential

factor upon the dark test. The statistical treatment of these data showed that the observed and theoretical frequencies were so close that the chance of diet influencing the Bio-photometer readings was almost nil.

Although the practice factor was considered very important, particularly in the examination of children, this was not apparent in the present series of adults. Occasionally patients were encountered who were unable to follow simple instructions, and these readings were discarded immediately. Practically the same percentages were found, whether or not more than one test was performed.

Clinical night blindness always has been reported with greater frequency in men than in women and the greater exposure of men to sunlight had been considered to be the cause (Aykroyd, 1930). In the present study there were no essential differences between men and women.

Since visual purple is a pigment, several attempts have been made to correlate general pigmentary changes with dark tests. Even blondes, brunettes and red-heads have been compared by Getz et al. in 1939. In this series, negroes were found to have better adaptation than whites. There was, however, no increase in normal dietary intake in the colored race over the whites. There was a difference in ages, the negroes being the younger. Whereas earlier reports favored the view that pigmentary changes influenced adaptometer results, Birch-Hirschfeld (1917) and Birnbacher (1927) reported no relation of hair or eye color to dark test ability. Bunge and Heyn (1938) reported that adaptometer tests in eight cases of albinism showed curves similar to the pigmented controls.

Numerous attempts have been made to link poor adaptometer performances with diseases and other processes. Disease of the liver (cirrhosis), endocrines (hyper- and hypothyroidism), ulcerative colitis, pregnancy, etc., all have been made responsible for poor dark tests. In these routine clinic patients, unchallengeable diagnoses could not be made of such definite clinical syndromes with great enough frequency to permit statistical comparisons. It was not doubted that among the patients studied some degree of cirrhosis might be present.\* Definite diagnoses of cirrhosis did not occur, however, and, therefore, no figures could be obtained comparable to the works of Park (1935, 1936), Haig, Hecht and Patek (1938), Feldman (1938), Patek and Haig (1939).

Blood pressure determinations were available on almost any series of patients. Since this represented chronic disease, the attempt was made to compare the dark test and blood pressure readings. Surprisingly enough, this association was found to be close. There was about one million and a half to one chance in favor of the relationship. In other words, it appeared extremely likely that blood pressure levels affected Bio-photometer readings.

Further analyses on this present group revealed that age carried with it

\*It is interesting here to speculate upon the effect of age and changes in the liver. Schnitker and Hass (1934) found that 36 per cent of patients averaging 52 years of age at death had at least microscopic changes in the liver.

an ever increasing liability to hypertension. In addition, it was discovered that the incidence of normal and deficient dietary intakes remained practically the same throughout the various decades. Now, a further correlation remained to be made between the dark adaptation test and age. This association was significant. Restated, this meant that dietary factors (vitamin A) had no influence upon Bio-photometer readings but that age was most important. The older the individual, the less likely were his chances of having a normal dark adaptability.

The literature contained numerous references to the age factor and vision in dim light. Although Selling (1939) was of the opinion that the glare sensitivity did not increase with age, most workers who had tested adults for dark adaptation concluded that age definitely increased the threshold for dim light. However, where further comment was made, the occurrence usually was dismissed lightly. Hecht and Mandelbaum (1939) stated that "there is a subtle shift in distribution of rod thresholds with age which deserves to be pointed out, but we lay no emphasis on it." They considered that a possible yellowing of the ocular media with age accounted for the more obvious change in the final cone threshold. It should be remembered that these authors were only reporting on a group of 110 university associated persons. Lindquist (1938) concluded that different standards should be set up for the various age groups, since his older individuals showed poorer adaptation ability. Ferree, Rand and Lewis (1934) and Ferree and Rand (1933, 1936) concluded that for best efficiency, workers should be segregated into groups by ages, so that light intensities might be increased more easily. Older individuals needed more light "to keep pace with the failing powers of the eye."

This was confirmed by the present work and agreed with the report of Birch-Hirschfeld (1916) who found among 300 patients examined the following distinct increase of disturbed dark adaptation values: first and second decades 11.6 per cent deficient, third decade 20 per cent, fourth decade 26 per cent and fifth decade 35 per cent. He mentioned sclerosis, coloring of the lens with age or possibly some occurrence within the retina as possible explanations.

Local diseases of the eye were ruled out in the present series and in many of the published reports. In addition, the changes in the visual ability seemed to play no part in this aging process, since refractive errors were found to have no effect upon the ability to perform the test.

The present material was reexamined to determine, if possible, if age accounted for the difference between the controls and the patients in dark test ability. The average age of the controls was 26 years and 75 per cent were normal. Inspection of figure 1 showed that only 40 per cent of the patients were normal in the third decade. Thus, the controls were considered definitely superior in their ability to perform the test regardless of age. Simple individual variations were responsible for most of these better performances.

An analogy may be drawn with an individual's ability to shoot straight. Given identical weapons and firing conditions, people will be found to vary tremendously in marksmanship. These same factors may be operating in the case of dark adaptometry. Kyrieleis (1938) remarked that strong and weak lightnesses were relative notions whose absolute values varied within markedly wide limits from person to person. These individual variations must play a large rôle in the reports in which children between narrow age limits were tested.\*

Another factor had been considered to be heredity. Habs (1938) approached this problem by a study of adaptometry in 20 identical and 20 non-identical twins. He found that the curve was very similar for identical twins, more so than for the other group. This he considered as proof of the inheritance of dark test ability. He raised the question of environmental and vitamin A factors but drew no conclusions. Wood (1938) stated that the Birch-Hirschfeld photometer was satisfactory for dark tests. Further, he felt that both vitamin A deficiency and strong light were necessary to produce night blindness. However, he was aware that not all individuals subjected to the same conditions became night blind. He attempted to explain this on the basis of heredity.

Recently the nervous system was mentioned as a factor in the adaptation process. Thus, Elsberg and Spotnitz (1938) reported that the time required for adaptation was dependent upon the rate of recovery in the nervous system from previous lighting. Schouten and Ornstein (1939), after excluding all purely physical or chemical possibilities, were led to the assumption that the retinal synapses had a part to play in the adaptive process. Lythgoe (1940) ingeniously suggested that a spread of synaptic connections might occur as dark adaptation proceeded. This tended to decrease finer discriminatory sensations.

The effect of vitamin A deficiency upon the nervous system is still in dispute. However, it was shown that oxygen affects the nervous system and the adaptation curves (Fischer and Jongbloed, 1936; McFarland and Evans, 1939; McDonald and Adler, 1939). Nagel's adaptometer had been used to show a direct proportion between the amount of hemoglobin and the dark test in 10 healthy and 11 anemic patients (Takayasu, 1934).

Frequently, pupillary width was mentioned as a factor in aiding dark adaptation. Mention should be made of the work of Phillips (1939) who found that a comparatively large pupil in the light or dark or both retarded the test. He stated: "Since there is a significant decrease in pupil diameter in the light with age, the slowing of the course of dark adaptation with age cannot be due to pupil variations. Pupil diameter in the dark also decreases

\* It was interesting to consider in this connection the work of Harris and Abbasy (1939) who employed the Birch-Hirschfeld photometer. They reported the following readings on poor children between the ages of 11 and 13: 43 per cent "normal," 34 per cent "slightly below normal," and 23 per cent "definitely subnormal." The present work with the Bio-photometer for the age group between 10 and 19 years showed: 50 per cent normal, 23 per cent borderline and 27 per cent abnormal. These results do not differ significantly.

with age." Sloan (1940) felt that accurate correction factors should be applied for pupil width in dark adaptation.

Fatigue undoubtedly played a part in dark tests. Wiersma (1901, 1902) studied the effects of fatigue on minimal impressions and found that attention fluctuated widely. He reported that low grade lights may be perceived on straining but these tended to disappear and to recur on further straining. Because of previous training, he found some persons able to perform better in the morning and others at night. Older persons showed fatigue fluctuations in wider ranges than younger persons. Wiersma explained his findings by postulating that the cause (*a*) might be nerve fatigue, (*b*) might be a tiring of the muscles of fixation and accommodation which permitted a new less sensitive part of the retina to be stimulated by light, and (*c*) might be central. In 1908, Rabinowitsch proved the effect of fatigue (increased previous lighting) upon the curves obtained with Nagel's adaptometer. The recent widespread interest in the fatigue phenomenon will undoubtedly confirm these old facts and bring new ones to light.

Birnbacher (1927) used Birch-Hirschfeld's apparatus and checked each test upon himself. He found that he varied so much from day to day that he cautioned against too exact interpretation of results. In this connection, it was interesting to speculate upon the laws of chance. As Jung (1938) pointed out: "Using an instrument whose readings are affected by large chance errors, an investigator examines, say, 100 subjects. He selects the 10 people whose performances on the test happen to be the poorest, and gives them some kind of treatment. Next day he reexamines the 100 subjects. The average performance of the 100 is exactly what it was the day before, but the 10 who did most poorly then are now found to have improved strikingly." Thus, in any test where great variability existed, the lowest performers tended to improve with repetitions and similarly, the highest performers tended to gravitate toward the mean. Jung suggested the name "centripetal drift" for this phenomenon of regression toward the mean.

It became necessary, then, to consider the test itself in an attempt to explain the discrepancies between the various workers in the field. It was apparent that there were two main measurements of the test. One concerned the ability of the eye to adapt itself to dim light and the other was the rate of this adaptation process. It was to this latter factor that most attention had been directed. Yet, there was published work to prove that the rate of dark adaptation was no function of vitamin A in the body (Hecht and Mandelbaum, 1938; Wald, Jeghers and Arminio, 1938; Lewis and Haig, 1939, 1940). These same workers had shown changes in the final rod threshold for minimal lighting to be dependent upon the vitamin A intake and reserves. Since even this had been questioned by other workers, notably Steffens, Bair and Sheard, 1939; Isaacs, Jung and Ivy, 1938, 1940, who were unable to confirm the claims of the above observers, the final answer on the question of the linkage of vitamin A and the dark test must remain open.



As concerns adaptometry, there can be no questions. The test measures the rate of dark adaptability of eyes but only with fair accuracy. This rate is dependent upon many factors as enumerated above: individual, hereditary, mental, nervous system qualifications dependent upon inherent abilities, oxygen consumption, retinal synapses, etc., and all of these factors change with age tending to become less acute with increasing years. This natural wearing out process has been remarked for many bodily functions. It has been assumed frequently that this rate of adaptation is a function of vitamin A, but proof for this point has not been produced. With so many variables, the use of the rate of adaptation alone as a measure of vitamin A in the body would seem to be in its simplicity highly optimistic.

### SUMMARY AND CONCLUSIONS

1. The literature concerning the dark adaptation test divides into three groups:
  - a. Authors who believe that delayed dark adaptation as measured by existing instruments means deficient vitamin A in the diet, in metabolism, or in the reserves of the body.
  - b. Authors who, using the same apparatus, find no correlation between vitamin A and the recorded ability to perform the dark test.
  - c. Authors, dubious of the positive correlation between vitamin A and performance on existing photometers, who have offered modified apparatus of their own.
2. The 700 ambulatory patients are random selections averaging 45.5 years.
3. The 80 controls are healthy adults (medical students, etc.) averaging 26 years.
4. Local ophthalmological conditions are excluded in all subjects. Thus, where present, poor dark tests are considered examples of so-called "essential hemeralopia."
5. Bio-photometer readings show:
  - a. The training factor to be negligible;
  - b. A higher percentage of controls having normal dark tests than patients but this could not be ascribed to a superior dietary intake;
  - c. Normal adaptation in higher percentage of patients receiving normal qualitatively estimated diets, though no strong association could be established statistically;
  - d. Sex has no effect upon vision in dim light whether diets are normal or deficient;
  - e. Negroes are significantly superior in dark test performances (average age of negroes less than whites);
  - f. Patients with hypertension exhibit a significantly higher percentage of poor dark tests;

- g. Increasing age influences dark adaptometry adversely.
6. The effect of various factors upon the dark test are discussed:
  - a. *Negatively*, vitamin A and the diet, sex, race and the training factor:
  - b. *Positively*, individual factors of age, mentality, fatigue, heredity, inherent abilities of the nervous system (oxygen consumption, retinal synapses, etc.).
7. Recommendations are made that further work with the rate and end values of dark adaptation (both rods and cones and nervous system influences) be performed to establish the physiologic basis for the test rather than accepting previous work on the importance of vitamin A.
8. A correction factor for age must be determined and applied in future work with adaptometers.
9. In the present state of knowledge of scotopic vision, the terms night blindness and poor dark adaptation tests should not be used synonymously.

The author wishes to acknowledge the kind help and criticisms of Drs. N. C. Gilbert, A. C. Ivy and F. T. Jung and to express appreciation for the excellent technical assistance of Miss Helen Gurley.

#### BIBLIOGRAPHY

- AYKROYD, W. R.: Beriberi and other food deficiency diseases in Newfoundland and Labrador, Jr. Hyg., 1930, xxx, 357.
- BIRCH-HIRSCHFELD, A.: Nachtblindheit im Felde, Deutsch. Ophth. Ges. Ber. Heidelberg, 1916, p. 197.
- : Ueber Nachtblindheit im Kriege, Arch. f. Ophth., 1916, xcii, 273.
- : Das Fünfpunktadaptometer und seine Anwendung, Ztschr. f. ophth. Optik., 1917, v, 44.
- : Weitere Untersuchungen ueber Nachtblindheit im Kriege, Ztschr. f. Augenh., 1917, xxxviii, 57.
- : Einige Bemerkungen zur Untersuchung Nachtblinder, Klin. Monatsbl. f. Augenh., 1918, ix, 53.
- BIRNBACHER, T.: Die epidemische Mangelhemeralopie (Sog. essentielle Hemeralopia), Abhandl. a. d. Augenh. u. ihr. Grenzgeb., 1927, iv, 1.
- BUNGE, E., and HEYN, W.: Zur Dunkeladaptation von pigmentarmen und albinotischen Augen, Klin. Monatsbl. f. Augenh., 1938, c, 178.
- DANIEL, E. P., and MUNSELL, H. E.: Vitamin content of foods. A summary of the chemistry of vitamins, units of measurement, quantitative aspects in human nutrition and occurrence in foods, U. S. Dept. Agriculture, Misc. Publication No. 275. June, 1937.
- DAVENPORT, C. B., and EKAS, M. P.: Statistical methods in biology, medicine and psychology, 4th Edition, 1936, John Wiley & Sons, Inc., New York.
- DORNBUSH, A. C., PETERSON, W. H., and OLSON, F. R.: The carotene and vitamin A content of market milks, Jr. Am. Med. Assoc., 1940, cxiv, 1748.
- ELDER, M., and EMERY, E. S., JR.: Food habits of the patient with peptic ulcer, Am. Jr. Digest. Dis., 1937, iv, 493.
- ELSBERG, C. A., and SPOTNITZ, H.: A theory of retinocerebral function with formulas for threshold vision and light and dark adaptation at the fovea, Am. Jr. Physiol., 1938, cxxi, 454.
- : The neural components of light and dark adaptation and their significance for the duration of the foveal dark adaptation process, Bull. Neurol. Inst., New York, 1938, vii, 148.

- FELDMAN, J. B.: An instrument for qualitative study of dark adaptation, *Arch. Ophth.*, 1937, xviii, 821.
- : Use of photometer in detecting latent avitaminosis A. *Proc. Round Table, Nutr. and Pub. Health*, 1938, xvi, 66.
- : Practice of dark adaptation, A review, *Arch. Ophth.*, 1938, xix, 882.
- : Dark adaptation, night blindness and glaucoma, *Arch. Ophth.*, 1939, xxii, 595.
- : Dark adaptation, its place in accident prevention, *Indust. Med.*, 1940, ix, 158.
- FERREE, C. E., and RAND, G.: A new type of instrument for testing the light and color sense, *Am. Jr. Ophth.*, 1931, xiv, 325.
- : The effect of intensity of illumination on the near point of vision and a comparison of the effect for presbyopic and non-presbyopic eyes, *Trans. I. E. S.*, 1933, xxviii, 590.
- FERREE, C. E., RAND, G., and LEWIS, E. F.: The effect of increase of intensity of light on the visual acuity of presbyopic and non-presbyopic eyes, *Trans. I. E. S.*, 1934, xxix, 296.
- FERREE, C. E., and RAND, G.: The use of variable illumination in the correction of the presbyopic eye, *Am. Jr. Ophth.*, 1936, xix, 238.
- : Pilot fitness for night flying, *Science*, 1939, lxxxix, 223.
- : Testing fitness for night flying, *Am. Jr. Ophth.*, 1939, xxii, 655.
- : An instrument for testing pilot fitness, *Jr. Aviation Med.*, 1939, x, 114.
- : A more nearly absolute method of testing and rating vision, *Arch. Ophth.*, 1940, xxiv, 292.
- FISCHER, F. P., and JONGBLOED, J.: Untersuchungen ueber die Dunkeladaptation bei herabgesetztem Sauerstoffdruck der Atmungsluft, *Arch. f. Augenh.*, 1936, cix, 452.
- FRIDERICIA, L. S., and HOLM, E.: Experimental contribution to the study of the relation between night blindness and malnutrition. Influence of deficiency of fat-soluble A vitamin in the diet on the visual purple in the eyes of rats, *Am. Jr. Physiol.*, 1925, lxxiii, 63.
- GETZ, H. R., HILDEBRAND, G. B., and FINN, M.: Vitamin A deficiency in normal and tuberculous persons as indicated by biophotometer, *Jr. Am. Med. Assoc.*, 1939, cxii, 1308.
- GRANIT, R., MUNSTERHJELM, A., and ZEWI, M.: The relation between concentration of visual purple and retinal sensitivity to light during dark adaptation, *Jr. Physiol.*, 1939, xcvi, 31.
- HABS, H.: Zwillingsphysiologische Untersuchungen ueber die Erbbedingtheit der alveolaren CO<sub>2</sub>-Spannung, der Geschmacksschwellen unter der Dunkeladaptation nebst einem Ueberblick ueber die bisherigen zwillingsphysiologischer Arbeiten, *Ztschr. f. menschl. Vererb. u. Konstitutionslehre*, 1938, xxi, 447.
- HAIG, C., HECHT, S., and PATEK, A. J., JR.: Vitamin A and rod-cone dark adaptation in cirrhosis of the liver, *Science*, 1938, lxxxvii, 534.
- HARRIS, L. J., and ABBASY, M. A.: The dark-adaptation test: its reliability as a test for vitamin A deficiency, *Lancet*, 1939, ii, 1299 and 1355.
- HECHT, S.: The dark adaptation of the human eye, *Jr. Gen. Physiol.*, 1920, ii, 499.
- : Nature of foveal dark adaptation, *Jr. Gen. Physiol.*, 1921, iv, 113.
- HECHT, S., and SHLAER, S.: An adaptometer for measuring human dark adaptation, *Jr. Optic. Soc. America*, 1938, xxviii, 269.
- HECHT, S., and MANDELBAUM, J.: Rod-cone dark adaptation and vitamin A, *Science*, 1938, lxxxviii, 219.
- : The relation between vitamin A and dark adaptation, *Jr. Am. Med. Assoc.*, 1939, cxii, 1910.
- : Dark adaptation and experimental human vitamin A deficiency, *Am. Jr. Physiol.*, 1940, cxxx, 651.
- ISAACS, B. L., JUNG, F. T., and IVY, A. C.: Vitamin A deficiency and dark adaptation, *Jr. Am. Med. Assoc.*, 1938, cxi, 777.

- : Clinical studies of vitamin A deficiency. Biophotometer and adaptometer (Hecht) studies on normal adults and on persons in whom an attempt was made to produce vitamin A deficiency, *Arch. Ophth.*, 1940, xxiv, 698.
- JEANS, P. C., BLANCHARD, E., and ZENTMIRE, Z.: Dark adaptation and vitamin A. A new photometric technic, *Jr. Am. Med. Assoc.*, 1937, cviii, 451.
- JUNG, F. T.: Centripetal drift: a fallacy in the evaluation of therapeutic results, *Science*, 1938, lxxxvii, 461.
- KRAUSE, A. C., and SIDWELL, A. E., JR.: The absorption spectra of visual purple and its photodecomposition products, *Am. Jr. Physiol.*, 1938, cxxi, 215.
- KYRIELEIS, W.: Untersuchungen ueber den Ablauf der Dunkelanpassung mit einem neuen Verfahren automatischer Schwellenwertaufzeichnung, *Arch. f. Ophth.*, 1938, cxxxviii, 564.
- LEWIS, J. M., and HAIG, C.: Vitamin A requirements in infancy as determined by dark adaptation, *Jr. Pediat.*, 1939, xv, 812.
- : Vitamin A status of children as determined by dark adaptation, *Jr. Pediat.*, 1940, xvi, 285.
- LINQVIST, T.: Studien ueber das Vitamin A beim Menschen, 1938, Appelbergs Boktryckeriaktiebolag, Uppsala.
- LYTHGOE, R. J., and PHILLIPS, L. R.: Binocular summation during dark adaptation, *Jr. Physiol.*, 1938, xci, 427.
- LYTHGOE, R. J.: The mechanism of dark adaptation. A critical résumé, *Brit. Jr. Ophth.*, 1940, xxiv, 21.
- MCDONALD, R., and ADLER, F. H.: Effect of anoxemia on dark adaptation of normal and vitamin A-deficient subject, *Arch. Ophth.*, 1939, xxii, 980.
- : Clinical evaluation of tests of dark adaptation, *Arch. Ophth.*, 1940, xxiv, 447.
- McFARLAND, R. A., and EVANS, J. N.: Alterations in dark adaptation under reduced oxygen tensions, *Am. Jr. Physiol.*, 1939, cxxxvii, 37.
- PARK, I. O.: Preliminary observations on vitamin A deficiency as shown by studies with visual photometer, *Jr. Oklahoma Med. Assoc.*, 1935, xxviii, 357.
- : Further observations on vitamin A deficiency as shown by studies with the visual photometer and clinically, *Jr. Oklahoma Med. Assoc.*, 1936, xxix, 129.
- : Significance of vitamin A deficiency, Editorial, *Am. Jr. Digest. Dis. and Nutr.*, 1936, iii, 193.
- PATEK, A. J., and HAIG, C.: The occurrence of abnormal dark adaptation and its relation to vitamin A metabolism in patients with cirrhosis of the liver, *Jr. Clin. Invest.*, 1939, xviii, 609.
- PEARL, R.: Introduction to medical biometry and statistics, Third Edition, 1940, W. B. Saunders Company, Philadelphia.
- PHILLIPS, L. R.: Some factors producing individual differences in dark adaptation, *Proc. Roy. Soc. London, S. B.*, 1939, cxxvii, 405.
- PILLAT, A.: Does keratomalacia exist in adults? *Arch. Ophth.*, 1929, ii, 256 and 399.
- : The frequency of deficiency diseases of the eye due to lack of vitamin A in a military camp north of Peiping, *Nat. Med. Jr. China*, 1929, xv, 585.
- : The main symptoms of the eye in vitamin A deficiency in adults, *Nat. Med. Jr. China*, 1929, xv, 614.
- : Production of pigment in the conjunctiva in night blindness, prexerosis, xerosis and keratomalacia of adults, *Arch. Ophth.*, 1933, ix, 25.
- : Avitaminosen und Hypovitaminosen, a) Vitaminmangelzustände 1) Mangel und Vitamin A. *Ernährungslehre, Grundlagen und Anwendung*, Stepp, 1939, W. Julius Springer, Berlin, p. 283.
- : Gibt es eine Kriegshemeralopie? *München. med. Wchnschr.*, 1940, lxxxvii, 225.
- POPPER, H.: Histological demonstration of vitamin A in rats by means of fluorescence microscopy, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 133.

- : Histological demonstration of vitamin A in the human liver by means of fluorescence microscopy, *Proc. Soc. Exper. Biol. and Med.*, 1940, cxxix, 442.
- RABINOWITSCH, S.: Ueber den Gang der Schwellenempfindlichkeit bei Dunkeladaptation und seine Abhängigkeit von der vorausgegangenen Belichtung, *Ztschr. f. Augenh.*, 1908, xix, 301 and 464.
- SCHNITKER, M. A., and HASS, G. M.: A histologic study of the liver in patients affected with peptic ulcer, *Am. Jr. Digest. Dis. and Nutr.*, 1934, i, 537.
- SCHOUTEN, J. F., and ORNSTEIN, L. S.: Measurements on direct and indirect adaptation by means of binocular method, *Jr. Optic. Soc. America*, 1939, xxix, 168.
- SELLING, L. S.: Abnormalities of the eye and their significance in traffic court cases, *Jr. Am. Med. Assoc.*, 1939, cxiii, 994.
- SLOAN, L. L.: Instruments and technics for the clinical testing of light sense. I. Review of the recent literature, *Arch. Ophth.*, 1939, xxi, 913.
- : II. Control of fixation in the dark-adapted eye, *Arch. Ophth.*, 1939, xxii, 228.
- : III. An apparatus for studying regional differences in light sense, *Arch. Ophth.*, 1939, xxii, 233.
- : IV. Size of pupil as a variable factor in the determination of the light minimum, *Arch. Ophth.*, 1940, xxiv, 258.
- STEFFENS, L. F., BAIR, H. L., and SHEARD, C.: Photometric measurements on visual adaptation in normal adults on diets deficient in vitamin A, *Proc. Staff Meet. Mayo Clin.*, 1939, xiv, 698.
- STEININGER, G., ROBERTS, L. J., and BRENNER, S.: Vitamin A in the blood of normal adults. The effect of a depletion diet on blood values and biophotometer readings, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2381.
- STEININGER, G., and ROBERTS, L. J.: Biophotometer test as index of nutritional status for vitamin A, *Arch. Int. Med.*, 1939, lxiv, 1170.
- TAKAYASU, A.: Experimentelle Untersuchung ueber den Einfluss der Anemia auf die Dunkeladaptation, *Zentralbl. f. d. ges. Ophth.*, 1934, xxx, 273.
- TASSMAN, I. S.: Dietary deficiency and ocular diseases, *Arch. Ophth.*, 1932, viii, 580.
- WALD, G.: Carotenoids and the visual cycle, *Jr. Gen. Physiol.*, 1935, xix, 351.
- WALD, G., JEGHERS, H., and ARMINIO, J.: An experiment in human dietary nightblindness, *Am. Jr. Physiol.*, 1938, cxxiii, 732.
- WESSELY, K.: Ein einfacher Apparat zur Messung der Adaptation, *München. med. Wchnschr.*, 1915, xlix, 1698.
- : AUSSPRACHE: *Deutsch. Ophth. Ges. Ber. Heidelberg*, 1916 p. 226.
- : Ueber Störungen der Adaptation, *Arch. f. Augenh.*, 1916, lxxxi, 53.
- : Ueber Störungen der Adaptation, *Ztschr. f. Augenh.*, 1916, xxxv, 344.
- WIERSMA, E.: Untersuchungen ueber die sogenannten Aufmerksamkeitsschwankungen, *Ztschr. f. Psychol. u. Physiol. der Sinnesorg.*, 1901, xxvi, 168.
- : Untersuchungen ueber die Sogenannten Aufmerksamkeitsschwankungen, *Ztschr. f. Psychol. u. Physiol. der Sinnesorg.*, 1902, xxviii, 179.
- WOOD, D. J.: Night blindness in eye disease—suggestions and speculations. The Doyne Memorial Lecture. *Trans. Ophth. Soc. U. Kingdom*, 1937-1938, pt. 2, lvii, 469.
- WOSIKA, P. H.: Night blindness of war, *War Med.*, 1943, iv, 331.

# THE EFFECT OF CERTAIN ANTACIDS IN MAN MEASURED BY A SIMPLIFIED METHOD FOR THE CONTINUOUS RECORDING OF GASTRIC pH \*

By N. E. ROSSETT, M.D., and JAMES FLEXNER, M.D., *New York, N. Y.*

IN a previous communication <sup>1</sup> we described a method for the continuous recording of gastric pH in man. At that time we were of the opinion that colloidal aluminum hydroxide † in 30 c.c. dosage made up to 200 c.c. with water, or 200 c.c. of milk alone, fulfilled the physiological criteria of an ideal antacid. It was also noted that the use of calcium carbonate or of magnesium salts caused a great initial rise in pH but that their buffering effect was of short duration.

In the present study we have extended our observations on antacids with the use of an improved method for the continuous recording of gastric pH. In the procedure as originally described a tube at least 5/16ths of an inch in diameter containing a glass electrode and accessory tubes was introduced into the stomach. It was necessary that the patient retain the tube during the entire period of observation. Another disadvantage was that this arrangement required frequent recementing of the glass electrode at the bottom of the stomach tube to avoid electrical leakage.

## METHOD

The mechanical difficulties previously encountered have now been obviated by leading gastric juices from the stomach by means of a No. 16 French duodenal tube to a standard commercial continuous flow electrode. This electrode is coupled with a Beckman pH meter and with the recording potentiometer and the pumping system which have previously been described.<sup>2, 3, 4</sup> Thus, only standard commercial equipment available on the open market was utilized.

A series of patients with gastrointestinal symptoms was studied on repeated occasions by the above method. Patient E. B., who had a duodenal ulcer, was used as a subject on five successive mornings and the findings in this series of experiments were typical. The effect of sodium bicarbonate 1 gm., calcium carbonate 1 gm., 200 c.c. of sweet milk, 200 c.c. of milk plus calcium carbonate 1 gm., and colloidal aluminum hydroxide 15 c.c. plus milk of magnesia 4 c.c. was studied. The patient's fasting gastric juice was removed and adjusted to a pH of 1.5, after which 35 c.c. were returned to the stomach as the control specimen. This specimen was cir-

\* Received for publication February 1, 1943.

From the Second (Cornell) Medical Division, Bellevue Hospital, New York, N. Y.

† The preparation amphojel was used.

culated around the electrode by means of the pumping system and a control tracing was made on the recording potentiometer. Then the various substances to be studied were added in 200 c.c. volumes.

### RESULTS

Figure 1 was made by superimposing the tracings obtained on the above patient on five successive mornings.

It will be noted from this figure that 15 c.c. of colloidal aluminum hydroxide plus 4 c.c. of milk of magnesia when added to 200 c.c. of water act

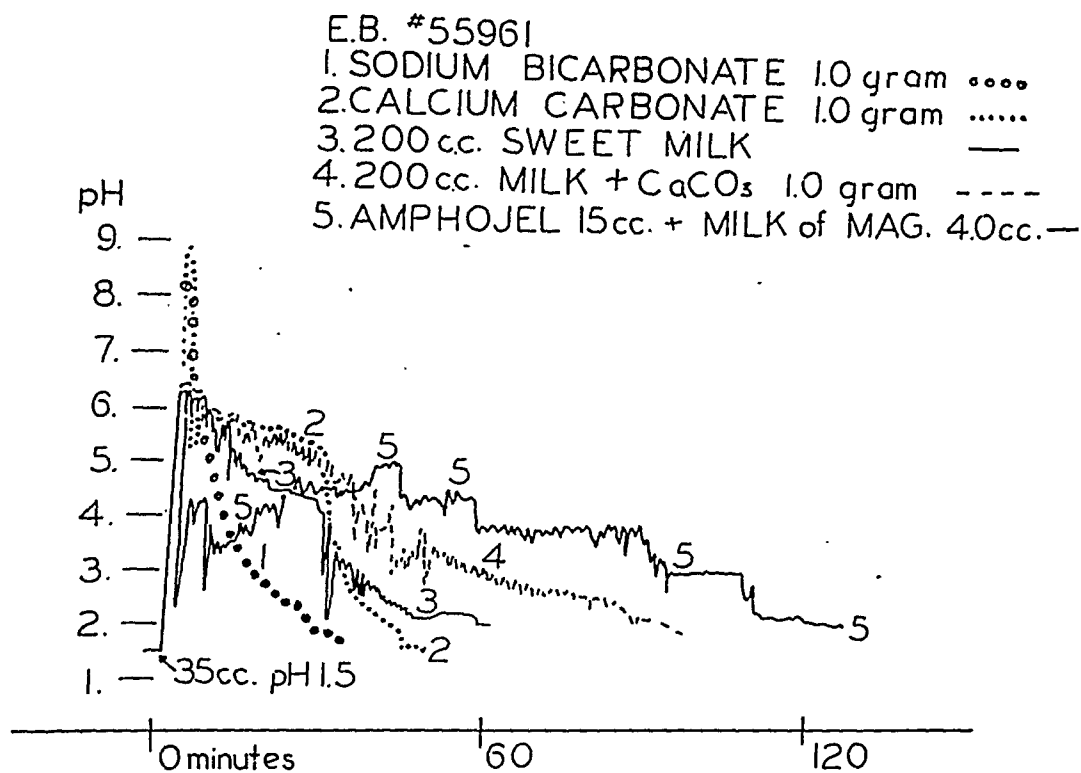


FIG. 1.

as an effective buffer for over two hours without carrying the pH above the upper limits of the physiological range.<sup>1</sup> It is also apparent that 200 c.c. of sweet milk reinforced by the addition of 1 gm. of calcium carbonate, are a more effective buffer than sweet milk, in the same quantity, when used alone.

### DISCUSSION

It is apparent from the above tracing that the addition of calcium carbonate to milk enhances the buffering properties of the milk, which, in turn, prevents the calcium carbonate from causing an excessive pH rise.<sup>1</sup> The prolonged effect of the combination would also avoid the often unpleasant necessity of repeated administration of milk alone at frequent intervals.

Similarly, the combination of milk of magnesia and colloidal aluminum hydroxide results in more prolonged effect than colloidal aluminum hydroxide alone,<sup>1</sup> with the subsequent necessity of smaller and less frequent doses. The undesirable initial rise in pH resulting from the use of milk of magnesia alone<sup>1</sup> is avoided, and the constipating effect of aluminum hydroxide is offset. The milk of magnesia content may be varied from 4 to 15 c.c. without raising the pH of the resultant mixture above 7.5, and affords a means of supplying any desired laxative action. This mixture has been used clinically on the Second (Cornell) Medical Division, Bellevue Hospital, with excellent results and will be reported in a later communication.

### SUMMARY

1. A simplified method for the continuous recording of gastric pH in the human being is described.

2. Amphoteric substances, such as milk and colloidal aluminum hydroxide, buffer alkalies, such as calcium carbonate and milk of magnesia, in their alkaline range.

3. Calcium carbonate 1 gm. in 200 c.c. of milk, and milk of magnesia 4 c.c., and colloidal aluminum hydroxide 15 c.c. in 200 c.c. of water, are long acting antacids.

4. The buffering effect of these combinations in the human being is readily demonstrated with this method.

### BIBLIOGRAPHY

1. ROSSETT, N. E., and FLEXNER, J.: A method for the continuous recording of gastric pH in situ. IV. Further evaluation of the efficacy of antacids in vitro and in the human being, *ANN. INT. MED.*, 1943, xviii, 193.
2. FLEXNER, J., KNIAZUK, M., and NYBOER, J.: A method for the continuous recording of gastric pH in situ, *Science*, 1939, xc, 239-240.
3. FLEXNER, J., and KNIAZUK, M.: A method for the continuous recording of gastric pH in situ. II. Experimental details, *Am. Jr. Digest. Dis.*, 1940, vii, 138-140.
4. FLEXNER, J., and KNIAZUK, M.: A method for the continuous recording of gastric pH in situ. III. Evaluation of the efficacy of certain antacids, *Am. Jr. Digest. Dis.*, 1941, viii, 45-47.



# CASE REPORTS

---

## PHEOCHROMOCYTOMA OF THE ADRENAL ASSOCIATED WITH PERSISTENT HYPERTENSION; CASE REPORT \*

By GEORGE W. THORN, M.D., F.A.C.P., JOSEPH A. HINDLE, M.D., and JOHN A. SANDMEYER, M.D., *Boston, Massachusetts*

For most patients with *persistent*, severe hypertension there is little hope of inducing a complete and uncomplicated cure. The classical syndrome of paroxysmal episodes of severe hypertension associated with pheochromocytoma of the adrenal gland is well known (Howard and Barker<sup>1</sup>). The fact that pheochromocytoma of the adrenal may at times be associated with a persistent, severe hypertension has been described by Kirshbaum and Balkin.<sup>2</sup> However, this fact is not generally appreciated. The present case is reported in view of a striking improvement in blood pressure which was associated with the removal of a pheochromocytoma in a patient who had been followed for several years with a diagnosis of "malignant hypertension."

### CASE REPORT

Patient J. M. B., a 40 year old white, married woman, entered the Peter Bent Brigham Hospital for the first time on April 2, 1943, with the chief complaint of headache and known hypertension of approximately seven years' duration. In 1934 she had had her first and only pregnancy which terminated in the birth of a normal, full-term child. During pregnancy, hypertension or signs of toxemia of pregnancy were not observed; systolic blood pressure readings did not exceed 120 to 130 mm. of Hg. In March 1937 during the course of a routine examination a striking elevation of blood pressure (220 mm. Hg systolic and 150 mm. diastolic) was discovered. Subsequent examinations confirmed this finding and the patient was referred to a hospital for more complete study. At that time her chief complaint concerned occasional severe headaches, often associated with nausea, rarely with vomiting. Physical examination revealed a blood pressure of 220 mm. Hg systolic and 120 mm. diastolic, heart of normal size without significant murmurs, and some narrowing of the arteries in the fundus oculi. No hemorrhages or exudates were noted at this time. Laboratory examinations, including urinalysis, kidney concentration tests, phenolsulfonphthalein excretion, blood urea nitrogen, serologic reactions, sedimentation rate, electrocardiogram, roentgenogram of the heart and basal metabolic rate, were not remarkable. Since no etiological factor was disclosed, a diagnosis of idiopathic malignant hypertension was made and a program of restricted activity with sedation was outlined.

In November 1937 because the headaches had become more severe, the patient was seen by another medical consultant who confirmed the earlier findings but in addition noted some blurring of the discs, increased light reflex along the retinal

\* Received for publication February 9, 1944.

From the Departments of Medicine and Surgery, Peter Bent Brigham Hospital and Harvard Medical School, Boston.

vessels and numerous fine white linear scars in both fundi. To complete the study an intravenous pyelogram was advised but was not performed at that time.

In March 1938 her case was again reviewed and no new changes were noted other than a progression of the alterations in the fundi now consisting of marked narrowing of the arteries, wide light streaks, tortuous and engorged veins, marked arteriovenous compression and numerous radial streaks interpreted as old hemorrhages. During the intervening five years (1938-1943) no new symptoms had developed other than increased fatigue on exertion. The headaches were promptly relieved in the prodromal stage by empirin and codeine. The blood pressure was found consistently to be elevated, ranging from 200 mm. Hg systolic and 150 mm. diastolic to 260 mm. systolic and 160 mm. diastolic. No paroxysms of increased hypertension were noted, nor was her blood pressure ever observed to be within normal range. In 1943, before considering the possibility of sympathectomy for the relief of hypertension, intravenous pyelography was performed. This revealed that the left kidney was abnormally low in position with a soft tissue mass above it. A tentative diagnosis of adrenal tumor was made and the patient was referred to this hospital for further diagnosis and recommendation. Inquiry at this time (1943) revealed no history of paroxysmal attacks of palpitation, sweating, tremor, dizziness or weakness. There were no cardiopulmonary complaints other than fatigue and shortness of breath on moderate exertion. The family history revealed that her father had died of coronary occlusion, that two of his siblings suffered from angina pectoris, that her mother had hypertension and that one of the patient's sisters died in infancy of a congenital heart lesion. The past history of the patient revealed that she had always been in good health up to the onset of the present illness.

*Physical examination* on admission to the Peter Bent Brigham Hospital on April 2, 1943, revealed a well-developed and well-nourished white woman in no acute distress. Weight was 58.6 kg., temperature 98.6° F., pulse rate 80 per min., respirations 20 per minute, and blood pressure 270 mm. Hg systolic and 160 mm. diastolic in both arms. The arteries of the fundus oculi were very narrow with a sharp light streak; the veins were distended and tortuous; there was striking arteriovenous compression and small white lines radiating from the discs with no evidence of recent hemorrhages, exudates or papilledema. The heart was slightly larger than normal. The first heart sound at the apex was accentuated; the aortic second sound was exceedingly loud and ringing; there were no murmurs, and the heart rate was regular. The chest was clear. There were no abdominal striae, and no masses could be felt in the abdomen; external genitalia were normal; pelvic, rectal and neurological examinations were not remarkable. There was no edema of the extremities. The blood pressure in both legs was 250 mm. Hg systolic and 150 mm. diastolic to 270 mm. systolic and 160 mm. diastolic. Hair distribution over the body was of normal female type; there was no acne. Adipose tissue was generally distributed over the body.

*Laboratory examination:* Blood Hinton and Wassermann reactions were negative. Urinalysis revealed a specific gravity varying from 1.010 to 1.015, a slight trace of albumin with occasional red blood cells, white blood cells, hyaline and granular casts. Red blood cell count was 3.8 million, hemoglobin 12.4 gm., hematocrit 37 per cent volume packed cells, white blood count 5.8 thousand with a normal smear and differential count. Blood chemical studies revealed a blood urea nitrogen of 14 mg., non-protein nitrogen 23 mg., serum protein of 7.3 gm., serum albumin 3.9 gm., serum globulin 3.4 gm., blood sugar 81 mg., and blood cholesterol of 235 mg. per 100 c.c. Serum chloride was 100 m. eq. per liter and carbon-dioxide combining capacity 28.2 m.M. Urine culture was sterile. Phenolsulphonphthalein test revealed 25 per cent of the dye excreted in 15 min. and a total of 50 per cent in two hours. Seventeen-ketosteroid excretion was 6.7 mg. and 7.3 mg. per 24 hours on two occasions (normal for adult females being 8 to 12 mg.). An oral glucose tolerance curve revealed a

fasting-blood sugar level of 130 mg. per 100 c.c.;  $\frac{1}{2}$  hour after ingestion of 100 gm. of glucose blood sugar was 100 mg., at 1 hour 68 mg., at 2 hours 77 mg. and at 3 hours 85 mg. Roentgenogram of the heart showed it to be transverse in position, prominent to the left with an elongated, tortuous aorta; on fluoroscopy there was a good regular beat with increased pulsation along the right border; the heart was 5 per cent above



FIG. 1. Tumor of the left adrenal region displacing left kidney downward.

average by height-weight ratio. An electrocardiogram revealed an abnormal form of ventricular complex with  $T_1$  and  $T_2$  diphasic and  $T_3$  inverted, Lead IV being normal. Stereoscopic films of the skull showed a vault of average thickness, with no localized changes or signs of pressure. The pituitary fossa was normal. A sodium amytal blood pressure depression test with the use of 0.4 gm. of the drug in a single dose was followed by a lowering of blood pressure from a level of 240 mm. Hg systolic and 140 mm. diastolic to 180 mm. systolic and 110 mm. diastolic.

Dr. Lewis Dexter attempted to recover epinephrine or epinephrine-like substances from the urine of this patient prior to operation. Employing the method of Richter<sup>3</sup> it was impossible to demonstrate any epinephrine-like activity before operation, or after operation at a time when the patient was receiving sizeable injections of adrenalin in aqueous solution and in oil.

An intravenous pyelogram disclosed prompt excretion following the injection of 20 c.c. of diodrast. It was apparent that the left kidney was much lower than normal in position and somewhat rotated. The excretion of dye was less complete on the left side than on the right. There was a large soft tissue mass visible above the left kidney (figure 1). The upper pole of the left kidney was not delineated to a satisfactory degree. A report on cystoscopic examination follows:

"The cystoscope was introduced with ease. The bladder wall was normal. No. 5 whistle-tipped catheters were passed up either ureter a distance of 28 or 29 cm. on the right, but on the left to only 25 cm. beyond which it would not pass, apparently this kidney being low. There was a good flow of urine from both sides. Microscopic inspection of both ureteral and bladder urines was negative except for a few red cells

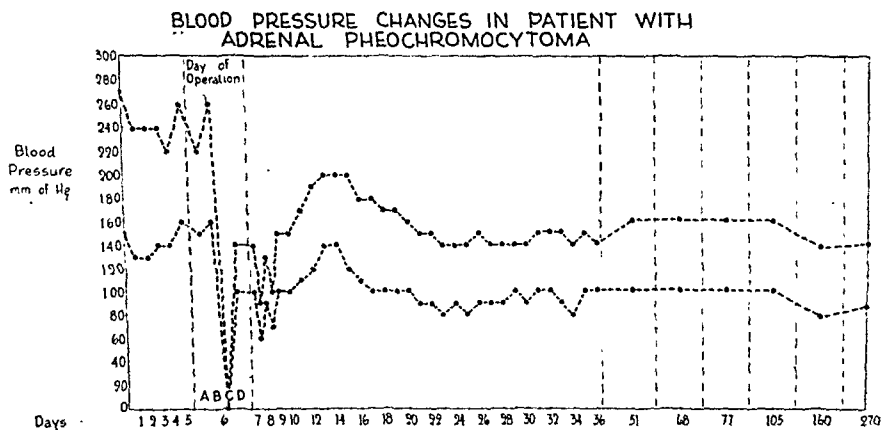


CHART 1.

on the right, apparently traumatic in origin. Cultures were taken from both ureteral urines and from the bladder urine, and divided function tests with PSP were made. This showed an appearance time of 3 minutes on the left and 3½ minutes on the right. The 10-minute volume was 8 c.c. on the right and 23 c.c. on the left. Dye excreted on the right in 10 minutes was 3.5 per cent; on the left, 5.5 per cent."

From these examinations it appeared probable that this patient was suffering from a tumor arising in the upper pole of the left kidney or adrenal region. In the absence of virilism, diabetes, osteoporosis, acne, abdominal striae and with a normal level of 17-ketosteroid excretion, a hyperfunctioning tumor of the adrenal cortex did not seem likely. The differential diagnosis thus was limited to:

(a) A tumor of the left kidney or adrenal coincidentally associated with hypertension or

(b) A tumor of the adrenal medulla (pheochromocytoma) responsible for *persistent* hypertension.

With the possibility of this latter diagnosis well in mind, the patient was transferred to surgery and precautions were taken to provide for the treatment of either acute adrenal cortical deficiency or acute medullary deficiency or both during and following operation.

*Operation:* (Dr. William C. Quinby) "Under ether anesthesia the region of the kidney was exposed through a transverse subcostal incision on the left. The kidney was found to be low, easily mobilized and of normal size. Above the left kidney the tumor was visible and palpable, attached to the upper pole. The superior and larger portion of the tumor had a well-developed capsule and was not adherent to the surrounding fat; the lower portion of the tumor was fixed to the kidney by adhesions of delicate character. Further dissection found that the blood supply of the tumor entered it at several points; the principal blood vessels, however, came from the renal pedicle. Toward the end of the operation, as the tumor was being mobilized and while the blood vessels were being severed one at a time, the patient's blood pressure began to fall, at first slowly and then precipitously until neither pulse nor blood pressure could be obtained—although 5 minutes previously blood pressure had been

TABLE I  
Summary of Specific Hormone Therapy for Collapse Which  
Followed Removal of Adrenal Tumor \*

Period	Adrenalin 1 : 1000	Adrenalin- in-Oil	Eschatin	Percorten	Other Medication
Acute collapse during operation	2 c.c. I.V. 2 c.c. S.C.	3 c.c. I.M.	30 c.c. I.V.		Transfusion whole blood.  Glucose and saline solu- tion I.V.
First day following operation	0.5 c.c. I.V. 3.0 c.c. I.M.	2 c.c. I.M.	20 c.c. I.V. 30 c.c. S.C.	10 mg. I.M.	I.V. plasma.  Glucose and saline solu- tion.
Second day following operation	0.5 c.c. I.V. 1.0 c.c. S.C.		20 c.c. I.V. 20 c.c. I.M.	10 mg. I.M.	
Third day following operation			20 c.c. I.M.		

\*I.V. = intravenous administration  
S.C. = subcutaneous administration  
I.M. = intramuscular administration

recorded as 240/160 mm. Hg. (See chart 1.) One c.c. of adrenalin was injected in the antecubital vein, 1.0 c.c. in the renal vein, and 2.0 c.c. subcutaneously; 3.0 c.c. of epinephrine-in-oil were injected intramuscularly; a transfusion of whole blood was begun and 30 c.c. of adrenal cortex extract were given together with the transfusion, since the size and state of the right adrenal was not known. Following this, systolic blood pressure was restored to a level of 150 to 170 mm. Hg. The tumor was completely removed, there being no evidence of involvement of regional lymph nodes or extension of tumor into any of the surrounding structures. At the close of the operation the patient's condition was entirely satisfactory, her blood pressure being 140/100 mm. Hg."

*Postoperative period:* The first 24-hour period following removal of the tumor was characterized by periodic episodes of hypotension (systolic pressure of 70 to 90 mm. Hg) which responded to epinephrine therapy, intravenous plasma and saline

olution, and for which relatively large doses of adrenal cortex extract were given, since the possibility of adrenal cortical insufficiency could not be eliminated. Between these periodic episodes of hypotension the systolic blood pressure was maintained at a level of 110 to 140 mm. Hg. Specific therapy during the operation and for the three days following operation is summarized in table 1.



FIG. 2. Pheochromocytoma of the left adrenal (size: 9.3 cm. by 7 cm. by 6 cm.).

During the second, third and fourth days following operation the systolic blood pressure slowly stabilized between 130 and 140 mm. Hg, and the episodes of hypotension became less frequent and less marked (chart 1). Adrenalin and adrenal cortex extract therapy were gradually reduced during this period and were discontinued altogether on the fourth postoperative day (table 1). On the fourth and fifth days following operation the patient's temperature was elevated and atelectasis of the right lower lobe of the lung was noted. This subsequently cleared, and with the exception of a slight infection of the wound, the patient made an uneventful recovery. She

was discharged from the hospital four weeks following operation, at which time her blood pressure (resting in bed) was 130 mm. Hg systolic and 80 mm. diastolic. Subsequent examinations (chart 1) reveal that her blood pressure has continued to remain at this level. When up and about and when examined after a rest period blood pressure readings averaged 160 mm. Hg systolic and 100 mm. diastolic.

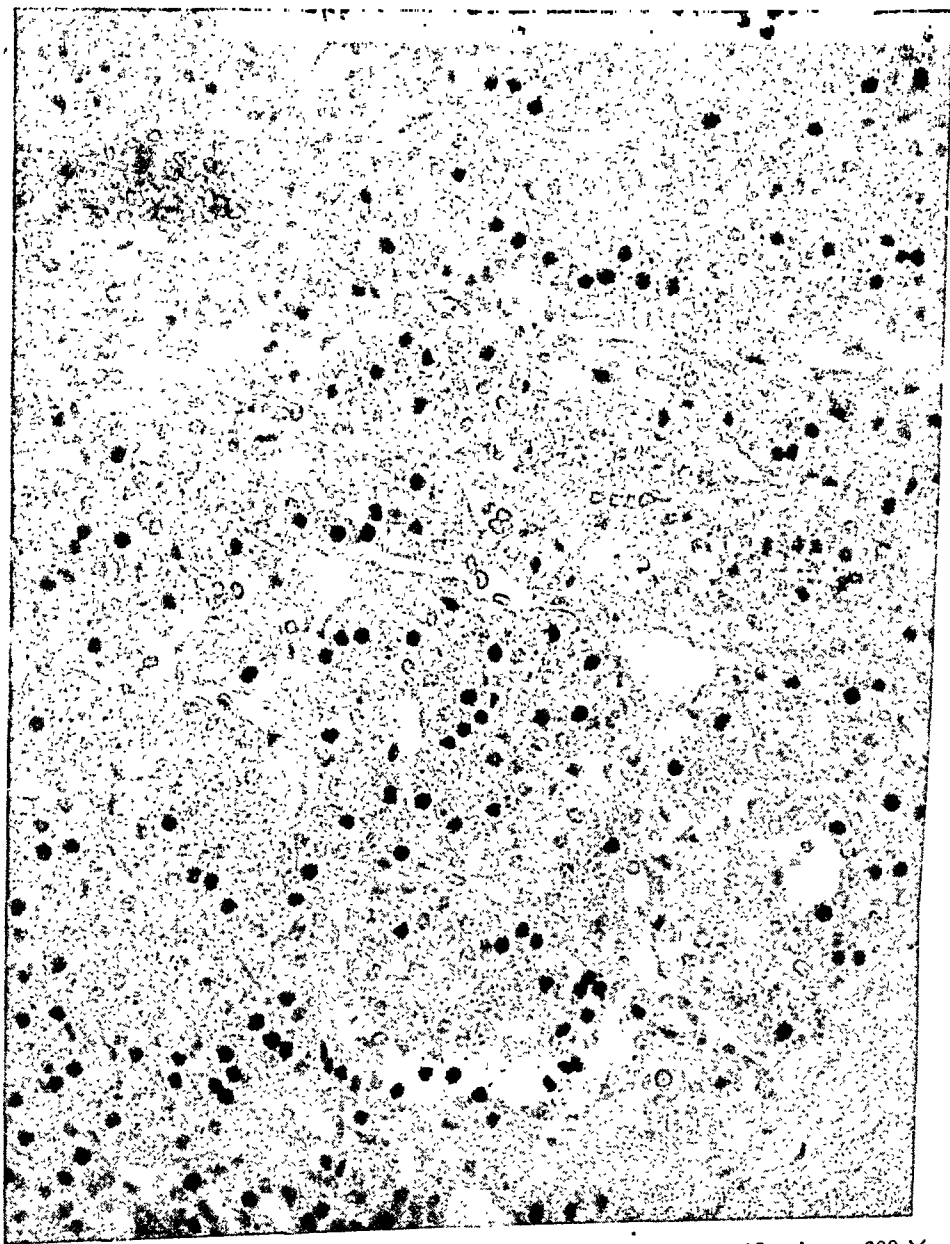


FIG. 3. Photomicrograph of adrenal pheochromocytoma. Magnification: 300 X.

Retinal examination revealed a progressive disappearance of the high-grade changes in the fundi which were noted upon admission. On the day following operation a few fresh hemorrhages were noted; since that time no new hemorrhages have been observed. There has been a gradual increase in the size of retinal arteries until at present they approach the normal in caliber and appearance.

*Pathological report:* (Dr. Clinton V. Z. Hawn). The tumor measured 9.3 cm. by 7 cm. by 6 cm. and weighed 220 gm. (figure 2). The tumor mass appeared to be well encapsulated and at one pole adrenal tissue appeared to be embedded. The cut surface was deep purple in color and apparently congested with a considerable amount of blood. Histologically the tumor tissue varied greatly from area to area. Characteristically the tumor cells were arranged in rounded masses which were separated by fine strands of connective tissue among which were numerous endothelial lined spaces (figure 3.). The individual cells were large, polyhedral or elongated which on Schmorl's staining showed fine granules of an olive green color revealing their chromaffin nature. In many areas the tumor had undergone degeneration. In some areas there had been extensive invasion of the capsule by the tumor masses and in some places extracapsular extension.

*Analysis of tumor for epinephrine content:* Through the courtesy of Dr. D. K. Kitchen of Parke, Davis and Company, a specimen of this tumor was analyzed for its epinephrine content. The tumor had been kept frozen since its removal, but unfortunately was not iced when forwarded to Detroit, Michigan, during the early summer. Therefore, the analyses of epinephrine probably represent only a fraction of the concentration which was originally present in the tumor.

"The extract of wet gland, representing a yield of 60 c.c. from 27 gm. of tissue (total tumor weight = 220 gm.) has been tested for adrenalin content and each c.c. found to be equivalent to 0.275 mg. of standard adrenalin. The action of the extract was definite, and characteristic of adrenalin activity."

*Subsequent course:* Because of the nature of the histological changes, it was felt advisable to irradiate the region of the left kidney. Hence 27 roentgen-ray treatments, with a total dose of 5400 roentgen units, were administered. At present, the patient feels well, is able to carry on her own work at home; headaches have disappeared, and when last seen 270 days following operation she appeared to be in very good physical condition. Her blood pressure (resting in bed) is 140 mm. Hg systolic and 88 mm. diastolic.

## DISCUSSION

Surgical removal of adrenal tumors is likely to induce acute epinephrine or adrenal cortical deficiency depending, of course, upon the type of tumor. For patients with adrenal cortical tumor, without excessive hypertension, it is our custom to use adrenal cortical hormone therapy, prior to, during and following operation. The preparations and dosages which we use are similar to those employed in the treatment of acute adrenal crises.<sup>4</sup> In the case of a patient with excessive hypertension one hesitates to administer either adrenal cortical or adrenal medullary preparations preoperatively. For this reason, quick action is required when blood pressure begins to fall during the removal of the tumor. An immediate precipitous reduction in blood pressure at or about the time the tumor is removed suggests acute adrenal medullary deficiency rather than adrenal cortical deficiency. In treating the hypotension of patient J. M. B. we administered quantities of adrenal cortical extract large enough to correct adrenal cortical deficiency and then were relatively safe in assuming that a sudden drop in blood pressure during the postoperative period represented epinephrine deficiency and could be corrected by the prompt administration of this hormone. The use of adrenalin-in-oil, intramuscularly, was of great aid in providing for a more sustained rise in blood pressure.



## SUMMARY

The possibility of hypertension associated with pheochromocytoma of the adrenal must be considered in the differential diagnosis of patients with so-called "malignant hypertension."

Vascular changes resulting from long-standing hypertension may be reversed following restoration of blood pressure to a more nearly normal level.

Removal of an adrenal pheochromocytoma always presents the possibility of collapse from acute epinephrine deficiency as well as the possibility of inducing adrenal cortical insufficiency. Both may require immediate and heroic therapeutic measures.

## CONCLUSION

Pheochromocytoma of the adrenal must be thought of as a possible cause of persistent, severe hypertension. This is one form of severe hypertension which may be readily amenable to surgery. The occurrence of acute epinephrine deficiency during ligation of the veins leading from the tumor requires prompt therapy.

## BIBLIOGRAPHY

1. HOWARD, J. E., and BARKER, W. H.: Paroxysmal hypertension and other clinical manifestations associated with benign chromaffin cell tumors, *Bull. Johns Hopkins Hosp.*, 1937, lxi, 371.
2. KIRSHBAUM, J. D., and BALKIN, R. B.: Adrenalin-producing pheochromocytoma of the adrenal associated with hypertension. Report of three cases, *Ann. Surg.*, 1942, cxvi, 54.
3. RICHTER, D., and MACINTOSH, F. C.: Adrenaline ester, *Am. Jr. Physiol.*, 1941, cxxxv, 1.
4. THORN, G. W., DORRANCE, S. S., and DAY, E.: Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients, *ANN. INT. MED.*, 1942, xvi, 1053.

## A CASE OF TRANSIENT SUCCESSIVE PULMONARY INFILTRATION (LOEFFLER'S SYNDROME) ASSOCIATED WITH TRICHINIASIS \*

By JAMES F. SLOWEY, M.D., *Cleveland, Ohio*

IN 1932 William Loeffler,<sup>1</sup> professor of medicine at the University of Zurich, described the syndrome that bears his name. Subsequently, in 1934, he reported 12 additional cases at the Fourth International Radiological Congress in Zurich and additional ones in 1936, a total of 51 cases.

The salient features of the syndrome are transient, successive pulmonary infiltrations with eosinophilia. The pulmonary manifestations are variable, large or small areas of the lung being involved. It may be unilateral, bilateral, homogeneous or nodular. It may disappear in one area and become manifest in an-

\* Received for publication June 22, 1942.

other, the lesion being transient in character. The particular area involved usually clears within two weeks.

The patients are not severely ill, and the condition is often discovered in the course of a routine examination. The eosinophilia usually is at its height while the lung is clearing and may vary greatly in degree. Most of the cases reported have come from Switzerland,<sup>2</sup> occurring usually in the spring and summer. Two-thirds of the cases occurred in males. The syndrome has been attributed to various causative agents.

Loeffler was of the opinion that many of the cases were of tuberculous origin. Breton<sup>5</sup> says it occurs in 5 to 8 per cent of asthmatics, and Engel<sup>4</sup> had two cases of possible sensitivity to *ligustrum*, which flowers in May and June.

*Ascaris lumbricoides* was found in two cases by Wild.<sup>2c</sup> It was thought that the larvae penetrated the intestinal wall and were carried by the portal vein or the thoracic duct to the right heart, thence to the lung where they caused a local reaction with atelectasis and penetrated the alveoli and then were coughed or carried up and expectorated or swallowed. Another case is reported by F. Parkes Weber.<sup>7</sup> The patient, a 10 year old boy, had transient pulmonary infiltration with eosinophilia, and had previously passed *Ascaris lumbricoides*.

In most instances the condition is thought to be of an allergic nature. Kline and Young<sup>a, b, c</sup> have described a condition of the lungs due to a reversible allergic reaction in the bronchi and interstitial tissues in cases of bronchial asthma that could very well explain many cases of Loeffler's syndrome even though the causes of the allergy might be different, e.g., pollen, *Ascaris lumbricoides*, or some other agent.

In postmortem examination of the lungs in cases of bronchial asthma, they found dark red, meaty lungs which contained air. The bronchioles were prominent and thick, and the bronchi and bronchioles contained abundant tenacious greenish-yellow or grayish, viscid material. Microscopically, the lumina of the bronchi were filled with mucus in which there were numerous neutrophilic polymorphonuclears, eosinophiles, and mononuclear cells, some areas of bronchopneumonia, and other areas of hemorrhage. Whereas many of the patients with Loeffler's syndrome are not asthmatic, many of them give a history suggestive of allergy; and the above described type of pulmonary involvement, or some modification of it, is presumably the condition which is present in many of these cases. Because the patients are not critically ill and do not die from the illness, no autopsy material is available.

I wish to report a case of transient, successive, pulmonary infiltration, which was associated with *Trichinella spiralis*.

#### CASE REPORT

The patient was a rather obese, 47 year old female of Italian descent, and the mother of four children. She was admitted to St. Alexis Hospital, Cleveland, on November 3, 1940.

Three weeks previous to admission, she was treated at home for sore throat and acute coryza. At that time, she had no cough or pains in her chest. About 11 days before admission she began to complain of left upper lumbar backache and chest pains.

At this time, she had an occasional mild cough and slight elevation of temperature. She was treated with sulfanilamide by her family physician but did not improve.\*

*Hospital Course.* On admission, she was cyanotic and in respiratory distress. Perspiration was profuse. Her temperature was 103° F., with pulse rate of 108. The respiratory rate was 28, and the blood pressure reading 90 mm. Hg systolic and 60 mm. diastolic. Her throat was slightly injected. The heart was normal, and there was a slight dullness in the left base with fine râles in this area.

The laboratory examinations revealed the following. Estimation of the blood sulfanilamide 5.5 mg. per cent. White blood cells 22,000; red blood cells 4,810,000; hemoglobin 13 gm.; sedimentation rate, 120. Differential count: Polymorphonuclears, 67; small lymphocytes, 2; large lymphocytes, 3; eosinophiles, 23; monocytes, 4; basophiles, 1. Blood platelets, normal.

Sputum examination showed gram positive streptococci and gram positive diplococci and staphylococci. No Quellung observed with specific pneumococcic typing sera. The roentgenogram of the lungs showed the right lung to be clear, and on the left, "There is increased density over the base of the lung sufficient to obliterate lung detail, but the outline of the heart and the diaphragm are still visible."

The patient was given sulfapyridine, but this was discontinued after five days because of a definite decrease in the number of red blood cells. On the sixth hospital day the temperature was 99° F., and the lungs were clear on physical examination.

The following day numerous coarse râles developed in the right base and the temperature rose to 101° F. On the eighth hospital day, the patient developed a maculopapular pruritic rash on the face, chest and back, the voice became hoarse, and the temperature rose to 102° F. The chest findings remained the same. With no specific therapy, the rash disappeared and the temperature gradually decreased over a period of nine days.

On the tenth and thirteenth hospital days the stools were negative for ova and parasites.

The roentgenographic examination on the fifteenth hospital day showed a band-like area of density in the opposite lung, the left chest being clear.

The patient developed tenderness over the gall-bladder, and the liver increased in size, so that by December 9, her seventeenth hospital day, it was nearly down to the umbilicus. There was no jaundice, the icteric index being 4. The gastric analysis was normal. At this time her feet were slightly edematous.

By the twenty-first hospital day the liver receded to practically normal size, the temperature had dropped to normal, and both lungs were clear. The patient was discharged on December 18, her twenty-sixth hospital day, with a normal temperature. However, she still complained of muscular pains in the arms and legs and would sweat profusely on exertion.

The differential blood counts and sedimentation rates were as follows:

Hosp. Day	Date	W.B.C.	R.B.C.	Hgb.	Eos.	Sed. Rate
Adm. 1	11-23-40	22,000	4,810,000	13 gm.	23%	120
3	11-25-40				16%	
5	11-27-40		4,600,000			
7	11-29-40		3,240,000			
12	12- 4-40				8%	85
14	12- 6-40	11,000	4,600,000	13 gm.	10%	95
	1-21-41		3,730,000		34%	
	4- 8-41	8,900			13%	

\* This patient was referred to me through the kindness of J. N. Rini, M.D., the family physician.

Hosp. Day	Date	T. (rectal)	P.	R.	Rash	Sputum	Cough	Cyanosis	Lungs	Liver	Stool
1	11-23-40	103.4°	108	28		Strep. gram pos.; diplococci gram pos.; no pneumococci; bacilli; no acid fast B.	Mild	Marked	Right, clear; left density; left base râles; x-ray confirmation		
3	11-25-40	101.4°	112	32							
6	11-28-40	99°	100	28				Still present	Clear		
7	11-29-40	101°	108	24					Coarse râles; right base		
8	11-30-40	102°	120	32	+				Coarse râles; right base		
10	12- 2-40	101.4°	96	32							Neg. for ova and parasites
13	12- 5-40	101.2°	112	24							Neg.
15	12- 7-40	101°	120	26					X-ray: density right base; left lung, clear		
17	12- 9-40	99.8°	100	24						Large	
20	12-12-40	100.2°	94	24		Strep. gram pos.; diplococci gram pos.; no pneumococci; bacilli; no acid fast B.					
21	12-13-40	99°	92	24					Both lungs, clear		
	1-21-41							Slight	Both lungs, clear	Normal	

At home, the patient gradually improved. The muscle pains decreased and the sweating became less.

She was prevailed upon to have a muscle biopsy, which was done on April 15. Approximately 100 larvae of *Trichinella spiralis* per 1 gm. of deltoid muscle were found, a number sufficiently large to cause clinical symptoms.

### DISCUSSION

This patient at no time had early signs of *Trichinella spiralis* infestation such as puffy eyelids or swelling of the face. There were at no time attacks of diarrhea or epigastric distress, which are usually found with trichiniasis. She did not like ham and was not in the habit of eating it, with the exception that occasionally she ate a little spiced ham in a sandwich.

On admission she had a pulmonary lesion on the left that had been present probably less than 11 days and that cleared six days after admission to the hospital. She then developed consolidation on the other side that cleared in nine days. An eosinophilia was present throughout her illness. At no time was the condition of the patient critical.

I feel that the transient successive pulmonary infiltrations with eosinophilia found in this case were due to an allergic reaction of a reversible type in the bronchi and interstitial tissue of the lungs. Such a reaction could be due either to blood-borne *Trichinella spiralis* antigen causing the local pulmonary reactions or to antigen from trichinella present in the local area of the lung. There is valid immunological evidence that the same type of local reaction could be produced in either event.

The incidence of *Trichinella spiralis* infestation in this country is estimated as being about 20 per cent,<sup>8</sup> varying in different parts of the country. This figure is arrived at by estimation from reports on autopsy findings using both the direct microscopic examination of compressed muscle from the diaphragm, or the diaphragm and some other muscle, and by the Baerman digestive method. A great many of the cases are of the subclinical type, having less than 100 larvae per gram of muscle. In areas where the pigs and hogs are fed on garbage the incidence is higher. Beaver, bear, rats and other animals may be infected.

In spite of the fact that the meat undergoes inspection, many people become infected with *Trichinella spiralis* because of eating infected pork that has not been sufficiently cooked.

Besides the cases reported in this country, there have been cases reported from practically everywhere in the world including Switzerland,<sup>9</sup> whence most of the cases of Loeffler's syndrome have been reported.

In reviewing the literature, there is a relationship between pulmonary disease of Loeffler's syndrome type and trichiniasis. The last case in the series of six reported by C. Maier<sup>9a</sup> was a case with transient pulmonary infiltrations which were accompanied by eosinophilia, but in which trichinae could not be found on muscle biopsy, and it was consequently considered to be a case of Loeffler's syndrome. This may have been a case of trichiniasis with a low grade infestation, the trichinae being so few in number that none was in the specimen of muscle examined.

Several other cases of trichiniasis have been reported having pulmonary symptoms or signs.<sup>10</sup> However, in most of these cases, the pulmonary involvement was slight and was not a prominent feature of the infestation. The first case of trichiniasis reported in detail in the group presented by Minot and Backman had transient pulmonary infiltrations of short duration, and if the trichinae had not been looked for or found, could easily have been considered a case of Loeffler's syndrome of unknown etiology.

#### CONCLUSIONS

1. A case is presented with the findings of Loeffler's syndrome associated with *Trichinella spiralis* infection.
2. Similar cases taken from the literature are cited.
3. Trichiniasis is found occasionally in Switzerland.
4. The majority of the cases of Loeffler's syndrome are reported from Switzerland.
5. Cases of Loeffler's syndrome should have skin tests for trichiniasis and should have ample biopsy sections of muscle examined by the slide compression method for *Trichinella spiralis*.

#### BIBLIOGRAPHY

1. LOEFFLER, W.: (a) Zur Differential-Diagnose der Lungeninfiltrierungen: II. Ueber flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk., 1932, lxxix, 368-382.  
(b) Die flüchtigen Lungeninfiltrate mit Eosinophilie, Schweiz. med. Wchnschr., 1936, lxxvi, 1069-1078.
2. (a) GEIGER, H.: In discussion on LOEFFLER.<sup>1b</sup>  
(b) OERI: In discussion on LOEFFLER.<sup>1b</sup>

- (c) LEITNER, J.: Ueber flüchtige hyperergische Lungeninfiltrate mit Eosinophilie bei Tuberkulose, *Beitr. z. Klin. d. Tuberk.*, 1936, lxxxviii, 388-420.
- (d) ROSSEL, G., and HOURIET, J. H.: Infiltrations pulmonaires fugaces successives avec éosinophilie sanguine, *Jr. méd. de Leysin*, 1937, xv, 245.
- (e) WILD: In discussion on LOEFFLER.<sup>1b</sup>
- (f) STEIGER, J., and ROHNER, H.: Flüchtige Lungeninfiltrierungen mit Eosinophilie, *Deutsch. Tuberk.-Blatt.*, 1937, xi, 154-158, in discussion on LOEFFLER.<sup>1b</sup>
3. HANSSON, N.: Transitory lung infiltration with eosinophilia, *Acta radiol.*, 1937, xviii, 207-212.
4. ENGEL, D.: Anaphylaktisches Frühjahrsödem der Lunge. Eine pseudoepidemische Erkrankung, *Med. Klin.*, 1935, ii, 1466. Ueber eine eigenartige anaphylaktische Erkrankung der Lunge, *Beitr. z. Klin. d. Tuberk.*, 1935, lxxxvii, 239-250.
5. BRETON, A. (quoted by C. S. BARKER of Montreal): Transitory lung infiltrations associated with eosinophilia, *Canad. Med. Assoc. Jr.*, 1939, xI, 494-495.
6. (a) KLINE, B. S., and YOUNG, A. M.: Cases of reversible and irreversible allergic inflammation, *Jr. Allergy*, 1934-1935, vi, 247-257.
- (b) KLINE, B. S., and YOUNG, A. M.: Bronchial asthma, *Jr. Allergy*, 1934-1935, vi, 258-272.
- (c) In a discussion of the paper by GEORGE L. WALDBATT he states that he has observed patients who had pneumonia, within six to eight hours after an injection of serum was given, that he feels to be a noninfectious pneumonia based on an Arthus phenomenon in the lungs similar to that described by the authors as found in the appendix.
7. WEBER, F. PARKES: Transient pulmonary infiltration with blood eosinophilia, *Brit. Jr. Child. Dis.*, 1939, xxxvi, 15-17.
8. (a) KUITUNEN-EKBAUM, E.: Incidence of trichinosis in humans in Toronto, *Canad. Pub. Health Jr.*, 1941, xxxii, 569-573.
- (b) KERR, K. B., JACOBS, LEON, and CUVILLIER, EUGENIA: Studies on trichinosis, etc., *Pub. Health Rep.*, 1941, lvi, 836-855.
- (c) EVANS, C. H., JR.: Trichinosis in Cleveland, *Jr. Infect. Dis.*, 1938, lxiii, 337-339.
- (d) MELENEY, HENRY E.: Trichinosis in human diaphragms in Nashville, Tennessee, *Am. Jr. Hyg., Section D.*, 1941, xxxiv, 18-22.
9. (a) MAIER, C.: Zur Kenntnis der Trichinose, *Schweiz. med. Wchnschr.*, 1937, xviii, 248-250.
- (b) TANG, C. E.: Trichinella infection in rats in Fakién, *Clin. Med. Jr.*, 1939, lv, 537-541.
- (c) HALIEN, L. G.: Epidemic in Lindenburg, Sweden, 40 cases, *Acta. med. Scandinav.* 1938, xciv, 355-365.
- (d) SCHEIFLY, C. H.: The prevalence of trichiniasis, *Am. Jr. Hyg.*, 1938, xxvii, 142-148.
10. MINOT, G. R., and BACKMAN, F. M.: Respiratory signs and symptoms in trichinosis, *Am. Jr. Med. Sci.*, 1915, cl, 571-582.

### A CASE OF NITROBENZENE POISONING\*

By ZOLTON T. WIRTSCHAFTER, M.D., Major, MC, AUS, F.A.C.P., *Cleveland, Ohio*, and RALPH WOLPAW,† M.D., Major, MC, AUS, *Charleston, South Carolina*

NITROBENZENE, or Oil of Mirbane as it is known commercially, is a common solvent for a number of every day substances such as shoe polishes and dyes, lac-

\* Received for publication July 13, 1942.

† Stark General Hospital, Charleston, S. C.

quers, indelible inks, cheap perfumes, and a variety of other things. It is toxic to man by ingestion, direct contact, or inhalation or a combination of any of these avenues. Sollmann<sup>15</sup> states that a dose of as little as one gram may be fatal. The symptoms and signs of poisoning are nausea, vomiting, prostration, intense gray blue cyanosis, convulsions, and coma (Sollmann). As with other benzene derivatives, there is a direct toxic effect on the blood with rapid and intensive destruction followed in cases of recovery by active regeneration.

In view of the widespread use of substances containing this agent, cases of poisoning are probably more common than is generally believed. However, most of these cases are evidently mild and are probably diagnosed as acute indigestion or other functional upset. Recovery in these cases is rapid with symptomatic therapy. A moderate number of cases of more severe poisonings, either accidental or suicidal, have been reported in the literature. In most of these, the nitrobenzene has been taken orally. Spinner<sup>16</sup> reported 16 cases in women by whom the drug was used orally as an abortifacient in doses of 15 to 100 grams. Seven patients died and in only one case did an abortion result. He noted that recoveries had occurred after doses as large as 400 grams. Other authors<sup>2, 4, 12, 13, 18, 19, 20</sup> report recoveries from doses ranging from 3 to 100 grams. On the other hand, Muller<sup>9</sup> noted a case in which death followed ingestion of 25 c.c. of nitrobenzene, and Smith<sup>14</sup> reported a case which died following ingestion of 90 c.c. of marker ink containing nitrobenzene or aniline. Fullerton<sup>8</sup> cites one suicide from nitrobenzene, and the Office of the Chief Medical Examiner of New York City<sup>11</sup> records five deaths from ingestion of nitrobenzene in the four years from 1936 to 1939, inclusive. Of these, four evidently drank shoe polish or dye, and the fifth used a cleaning fluid containing nitrobenzene.

The largest number of cases of poisoning by contact was noted by Stifel<sup>17</sup> who reported 17 cases of severe cyanosis, headache, malaise, and vertigo following the wearing of freshly dyed shoes. The dye contained nitrobenzene and the etiology of the syndrome was confirmed by experiments on animals and men. Recovery in all cases was prompt. Erskine<sup>7</sup> noted four sisters who became ill following the use of a furniture polish containing nitrobenzene. Clark and Paul<sup>3</sup> report a case of poisoning occurring after the nitrobenzene was spilled on some wearing apparel. Poisoning in some of the contact cases was probably partially due to inhalation of the nitrobenzene which is moderately volatile. Dresbach and Chandler<sup>5</sup> showed that the effects of nitrobenzene fumigation on animals were largely nervous. There was an initial stimulation and then a paralysis of the motor centers of the skeletal muscles with little effect on circulation or respiration.

The authors had occasion to follow one case of nitrobenzene poisoning with recovery. The case is presented here.

#### CASE REPORT

M. M., a 30 year old white man, while on a drinking bout, ingested 15 c.c. of black laundry marker ink mixed with 15 c.c. of denatured alcohol. He remembered nothing after this and was brought into the hospital 11 hours later. Past history, family history, and social history were essentially negative except for a post-parotitic orchitis.

Physical examination revealed a well developed, thin, acutely ill, anxious and agitated white male with rapid, irregular, rattling respiration. There was a marked

generalized gray blue cyanosis with slate blue color of lips, nails, and tips of ears. The skin, particularly that of the forehead, was covered with a cold perspiration. The teeth, mucous membranes, and tongue were stained with dark blue material. The lungs were clear. The heart was normal in size, and the sounds were clear. The first sound was split at the apex but there were no murmurs. Pulses were rapid, thready, slightly irregular, and the rate was 140. The remainder of the examination including the neurological was essentially negative except for an atrophic right testis.

Laboratory findings on admission. Blood count: White cells 28,100; hemoglobin 85 per cent; red count 4.39 million; polymorphonuclears 73 per cent; lymphocytes 27 per cent; platelets 260,230. Two urine specimens showed a slight trace of albumin. Blood chemistry: Sugar 137 mg. per cent, non-protein nitrogen 32 mg. per cent,  $\text{CO}_2$  combining power 15.5 volumes per cent. Bleeding time was one and one-half minutes and clotting time three minutes. Fragility test showed hemolysis at .35 to .25 per cent saline. Serologic reactions were negative. Blood and urine were positive for anilin.

*Hospital course and treatment.* On admission, the patient was given caffeine subcutaneously followed by lavage with sodium bicarbonate solution. A continuous intravenous drip of 5 per cent glucose in normal saline was given. Oxygen and  $\text{CO}_2$  inhalations were also given because of the character of the respirations and the cyanosis. The patient improved gradually. His color returned to normal on the fourth hospital day, and the pulse and respiration reached normal levels on the third hospital day. There was a spiking temperature until the third day, followed by a slight elevation until the sixth day after which normal levels were maintained. The patient's further convalescence was uneventful except for an acute exacerbation of a chronic otitis media with a small amount of discharge. This responded readily to routine therapy. The patient was discharged in good condition on the fourteenth hospital day.

*Laboratory findings while in the hospital.* The  $\text{CO}_2$  combining power returned to normal in one day. The white cell count dropped to between 7,000 and 12,000 on the second hospital day. On the sixth hospital day the differential count showed polymorphonuclears 29, lymphocytes 66, monocytes 2, eosinophiles 2, basophiles 1; and two days later (eighth hospital day) polymorphonuclears 63, lymphocytes 30, monocytes 6, eosinophiles 1. Subsequent counts were essentially the same. A glucose tolerance test was normal. Blood cholesterol was 175 mg. per cent, and cholesterol esters 64 mg. per cent. Blood total proteins on three occasions varied from 4.5 to 5.5 per cent with a definite increase in the A/G ratio. Bromsulfalein liver function test showed 5 per cent retention in one-half hour. On admission the blood was dark brown in color and clotted very quickly. No examination for methemoglobin could be done at the time of admission but anilin was present for several days. One week later there was no methemoglobin present on spectroscopic examination. An electrocardiogram and urine concentration test done during the hospital stay were normal.

#### COMMENT

This case is of interest from several points of view. The ingestion of laundry marker or indelible ink is relatively uncommon. Smith<sup>14</sup> in his case report notes that the substance used was marking ink which contained anilin and probably nitrobenzene. His patient showed the classical picture of nitrobenzene poisoning with marked cyanosis, stertorous respiration, coma, and twitching of hands and feet. Death occurred 12 hours after ingestion. The manufacturers of the ink used in the case presented here reported that they knew of no other individuals who had taken their ink internally.<sup>10</sup>

The effect of the nitrobenzene on various organ systems is well illustrated in



this case. The most prominently involved was the circulatory system. Initially there was a marked cyanosis due largely to formation of methemoglobin, although this substance was not demonstrated because of lack of facilities. There were later changes in the differential cell count due to the direct toxic action of the poison. These were transitory and there was no appreciable effect on the red corpuscles. The hemodynamic changes were probably a result of the direct toxic effect of the nitrobenzene on the heart as well as of the anoxemia consequent to the low utilizable hemoglobin. They were manifested by signs of shock and a rapid, thready pulse. The rapid coagulation time and the color of the blood initially are findings which are difficult to explain. Similar findings were noted by other observers.<sup>7, 9, 12, 20</sup>

The respiratory system was also involved. The respiratory changes were probably the result of a direct toxic effect of the nitrobenzene on the respiratory center combined with the indirect effect resulting from the cerebral anoxemia associated with the massive formation of methemoglobin. The forced rapid respiration noted here accounts in large part for the low  $\text{CO}_2$  combining power obtained on the first day. In addition, there was an evident disturbance in acid base balance due possibly to toxic or dehydration changes.

The changes in the respiratory and circulatory systems were rather marked in contradistinction to the findings of Dresbach and Chandler<sup>5</sup> who note that respiratory and circulatory changes are minor. In their experiments, the major reactions were in the nervous system. Although this case does not show any outstanding nervous manifestation, other authors<sup>3, 4, 14, 16, 17, 19, 20</sup> have noted many nervous disturbances including paralysis, coma, involuntary movements, twitching, headache, vertigo, and irritability. Many of these symptoms and signs may have been due to cerebral anoxemia rather than a direct toxic effect.

The gastrointestinal tract was not noticeably upset in this particular case, although the fact that the patient was not seen immediately may account for the absence of gastrointestinal signs. Gastrointestinal symptoms and signs in nitrobenzene poisoning have been noted frequently in other cases<sup>3, 9, 17, 19</sup> and consist of nausea, vomiting, and abdominal discomfort. They are probably due in part to direct irritation and in part to central nervous system changes.

The liver was evidently definitely involved by the poison, although the denatured alcohol ingested may have contributed in some part to the changes in the liver despite the small amount of this substance taken. There were several findings which indicated decreased liver function. The low total protein with increased A/G ratio pointed to change in the liver which organ largely regulates the globulin fraction of the blood. In addition, there was a decrease in cholesterol esters also indicating liver damage, and last, the bromsulfalein test showed slight but significant retention. It is also possible that the decreased coagulation time and the increased viscosity of the blood may have been due partially to changes in the liver. Wright-Smith<sup>19</sup> noted changes in the urine which might have been attributable to liver damage (bile pigments).

Other organs and systems were not appreciably involved clinically. The pathological changes in the organs involved could not be determined in this case, but there have been various findings in autopsied cases and experimental animals dying from nitrobenzene poisoning.

The most common finding at autopsy was marked cyanosis of the skin and

viscera. The majority of cases showed considerable congestion of all organs, particularly the lungs, with occasional edema of the brain. In one case<sup>9</sup> there were multiple small hemorrhages in the heart, lungs, liver, kidneys, brain, and stomach, and in others there were erosions of the esophagus<sup>14</sup> and ecchymoses in the stomach.<sup>8</sup> Dresbach and Chandler<sup>6</sup> noted chromatolysis of Purkinje cells in animals poisoned with nitrobenzene. In the five cases from the Office of the Chief Medical Examiner of New York City<sup>11</sup> nitrobenzene was found chemically in all cases in either stomach, liver, brain, or blood. It was in the liver in four cases, the highest concentration being 62 mg. per 500 grams of liver. The concentration of nitrobenzene in the brain in the two cases in which the brain contained the substance was 82 mg. per 500 grams.

Treatment of nitrobenzene poisoning, like that of other poisons, consists generally of attempting to remove the poison or to hasten its excretion while at the same time using general supportive measures. In this case stimulation and lavage were used at first followed by intravenous glucose in normal saline and CO<sub>2</sub> and O<sub>2</sub> inhalations. The glucose was used to fortify the liver, the saline to replace that lost by vomiting and lavage and to aid in restoring the acid base balance. CO<sub>2</sub> and O<sub>2</sub> were given to stimulate respiration and also to attempt to decrease the cyanosis. Exsanguination followed by transfusion was considered but improvement was so rapid that it was not performed.

As a rule, the same general routine was followed in the treatment of the cases reported in the literature. The most important toxic effect of the nitrobenzene is in the formation of methemoglobin. Therefore, the reduction in the amount of methemoglobin formed and the prevention of its formation are highly desirable end results. Oxygen inhalation, the higher the concentration the better, is of value for these purposes; Brooks<sup>1</sup> has shown that intravenous glucose is effective not only in preventing methemoglobin formation but also in reducing methemoglobin already formed to hemoglobin which can then form oxyhemoglobin. Obviously, then, these two agents come as close to being specifics for the treatment of nitrobenzene poisoning as any known at present. Walterskirchen<sup>18</sup> cites one case of nitrobenzene poisoning treated with methylene blue intravenously. The patient recovered, but glucose was also used so that the exact value of the methylene blue cannot be determined. Pruett and Baum<sup>12</sup> noted the decreased coagulation time and the increased viscosity of the blood in their case and treated it with the usual method but in addition giving ex-sanguino transfusion followed by 500 c.c. of 4.5 per cent sodium citrate solution intravenously, the latter being used to reduce viscosity and increase coagulation time. In very severe cases of poisoning, the value of ex-sanguino transfusion is unquestionable, removing as it does the methemoglobin and the nitrobenzene and replacing these with utilizable hemoglobin. Stimulation and other supportive measures are always to be used as indicated by the individual case.

The recovery of this patient despite the relatively large and frequently fatal dose of nitrobenzene ingested is significant because it may possibly indicate the efficiency of the particular type of treatment used. However, as noted above, recoveries have occurred with much larger doses than this one when no specific routine of therapy was followed. Hence, it would seem that there is a large individual factor determining susceptibility to nitrobenzene and recovery from poisoning with this agent.

## CONCLUSIONS

Because of the wide range of use of substances containing nitrobenzene, poisoning with this agent is probably more common than is generally believed, although most cases are mild.

Nitrobenzene affects mainly the circulatory, respiratory, and central nervous systems both directly by toxic action and indirectly by formation of methemoglobin with resultant anoxemia. It also affects the liver and hematopoietic system causing damage by direct toxic action.

In the fatal cases, the major autopsy findings were marked cyanosis, marked congestion, and in a moderate number, multiple subserous hemorrhages. The nitrobenzene was found in liver, brain, stomach (washings usually), and blood.

The best treatment for nitrobenzene poisoning after the initial lavage is oxygen inhalation and intravenous glucose supplemented by stimulants, supportive measures, and ex-sanguino transfusions when indicated.

## SUMMARY

1. A number of cases of nitrobenzene poisoning from the literature are reviewed briefly.
2. A case of nitrobenzene poisoning is presented. The agent containing the nitrobenzene was laundry marker ink.
3. The case presented here and those in the literature are discussed from the viewpoints of clinical manifestations, pathological changes, and treatment.
4. A number of conclusions concerning nitrobenzene poisoning are made.

## BIBLIOGRAPHY

1. BROOKS, M. M.: Inhibition by glucose of methemoglobin formation, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxii, 63-64.
2. CISELL, E.: Vergiftung mit 100 grams Nitrobenzol; Heilung, *Med.-chir. Centralbl.*, Wien, 1894, xxix, 171. Abstract, *Lancet*, 1894, i, 1521.
3. CLARK, B. B., and PAUL, W. D.: Acute methemoglobinemia following exposure to meta-dinitrobenzene, *Jr. Iowa Med. Soc.*, 1935, xxv, 449-450.
4. DODD, A. H.: Poisoning by nitrobenzol: recovery, *Brit. Med. Jr.*, 1891, i, 849-850.
5. DRESBACH, M., and CHANDLER, W. L.: Some physiological disturbances induced in animals by nitrobenzol fumigation, *Proc. Am. Physiol. Soc.*, *Am. Jr. Physiol.*, 1917, xlii, 604-605.
6. DRESBACH, M., and CHANDLER, W. L.: The toxic action of nitrobenzene, with special reference to the cerebellum, *Proc. Soc. Exper. Biol. and Med.*, 1918, xv, 136.
7. ERSKINE, D.: Methaemoglobinemia in 4 sisters due to furniture polish (metadinitrobenzene) poisoning, *Guy's Hosp. Rep.*, 1931, lxxxi, 418-420.
8. FULLERTON, W. W.: Two rather uncommon fatal cases of poisoning; nitrobenzene poisoning, suicidal; sodium fluoride, accidental, *New England Jr. Med.*, 1930, cciii, 423.
9. MULLER, F.: Ueber Anilin-Vergiftung, *Deutsch. med. Wchnschr.*, 1887, xiii, 27.
10. Personal communication from B. Heller and Company, Chicago, Ill.
11. Personal communication from Dr. Milton Helpert, Assist. Med. Examiner, New York, N. Y.
12. PRUETT, W. V., and BAUM, E. E.: Nitrobenzol (oil of mirbane) poisoning, *Jr. Oklahoma Med. Assoc.*, 1929, xxii, 134-135.
13. SCOTT, R. W., and HANZLIK, P. J.: Poisoning by alcohol "denatured" with nitrobenzene, *Jr. Am. Med. Assoc.*, 1920, lxxiv, 1000.

14. SMITH, F. J.: A case of aniline poisoning, *Lancet*, 1894, i, 89-90.
15. SOLLMANN, TORRALD: A manual of pharmacology, 1936, W. B. Saunders Co., Philadelphia, pp. 623-624.
16. SPINNER, J. R.: Nitrobenzol not abortifacient, *Cor.-Bl. f. schweiz. Aerzte*, Basel, 1917, xlvii, 1439. Abstract, *Jr. Am. Med. Assoc.*, 1917, lxix, 2155.
17. STIFEL, R. E.: Methemoglobinemia due to poisoning by shoe dye, *Jr. Am. Med. Assoc.*, 1919, lxxii, 395-396.
18. WALTERSKIRCHEN, L.: Ein Fall von Mirbanolvergiftung, *Wien. klin. Wchnschr.*, 1939, lii, 317-318.
19. WRIGHT-SMITH, R. J.: Poisoning by nitrobenzene or "essence of mirbane" with recovery, *Med. Jr. Australia*, 1929, i, 867-868.
20. ZUCCOLA, P.: Nitrobenzene poisoning, 1918, *Policlinico*, Rome. Abstract, *Jr. Am. Med. Assoc.*, 1919, lxxii, 231.

---

## LONGEVITY IN VENTRICULAR ANEURYSM; REPORT OF A CASE FOLLOWED OVER A TEN YEAR PERIOD \*

By DENNISON YOUNG, Captain, MC, AUS, M.D., and JOHN B. SCHWEDEL, Lt. Comdr., (MC), U.S.N.R., M.D., F.A.C.P., *New York, N. Y.*

ALTHOUGH ventricular aneurysm may be compatible with good health and even with strenuous physical activity over a short period of time, it is most unusual that an individual with a progressively enlarging aneurysm of the left ventricle is able to continue his daily activity and maintain himself as a useful, productive member of society for a period of 10 years before succumbing to his underlying cardiac disease. The following case is reported because of the degree of well-being achieved over this number of years during which time the patient was closely followed clinically, radiographically and electrocardiographically.

### CASE REPORT

P. E., a 48 year old Russian-born machine operator in the cloak and suit industry, on September 24, 1931 developed severe epigastric pain radiating into both arms and a sense of tightness in the chest which lasted for 12 hours. A diagnosis of cardiac infarction was made. Morphine was administered and hospitalization was advised.

Mild glycosuria had been discovered 10 years previously, but on dietary restriction alone there had been no recurrence. There was no history of hypertension. He had been in good health until four months prior to this time when on exertion he developed episodes of pain in the epigastrium, chest and in both upper extremities, dyspnea and nausea. Medication afforded but temporary relief, and the attacks soon became more frequent and severe in character, never, however, so severe or prolonged as that on September 24, 1931.

When first seen he presented a picture of shock. The heart was not enlarged to percussion; the first apical sound was faint; a pericardial friction rub was present. The white blood cell count was 18,000 with 89 per cent polymorphonuclear leukocytes. A transient glycosuria was noted. The electrocardiogram was that of anterior wall infarction (figure 1 a).

\* Received for publication September 10, 1942.

From the Medical Service of the Montefiore Hospital, New York, N. Y.

The opinions and views set forth in this article are those of the authors, and are not to be construed as reflecting those of the United States Army or of the Navy Department.

The temperature rose to 101.6° F. the following day and remained slightly elevated for the subsequent month. The pericardial friction rub was more distinct on the second day but thereafter was no longer audible. On the fourth day there occurred a pulmonary infarction of the right lower lobe which was followed by a pleural effusion on the same side. His blood pressure fell from the initial 130 mm. Hg systolic and 80 mm. diastolic to as low as 88 mm. systolic and 60 mm. diastolic. His general condition improved slowly, and the heart sounds became less faint. Radiographic examination on October 13, 1931 revealed an enlargement of the heart to the right and left with a prominence at the mid-portion of the left border suggesting the

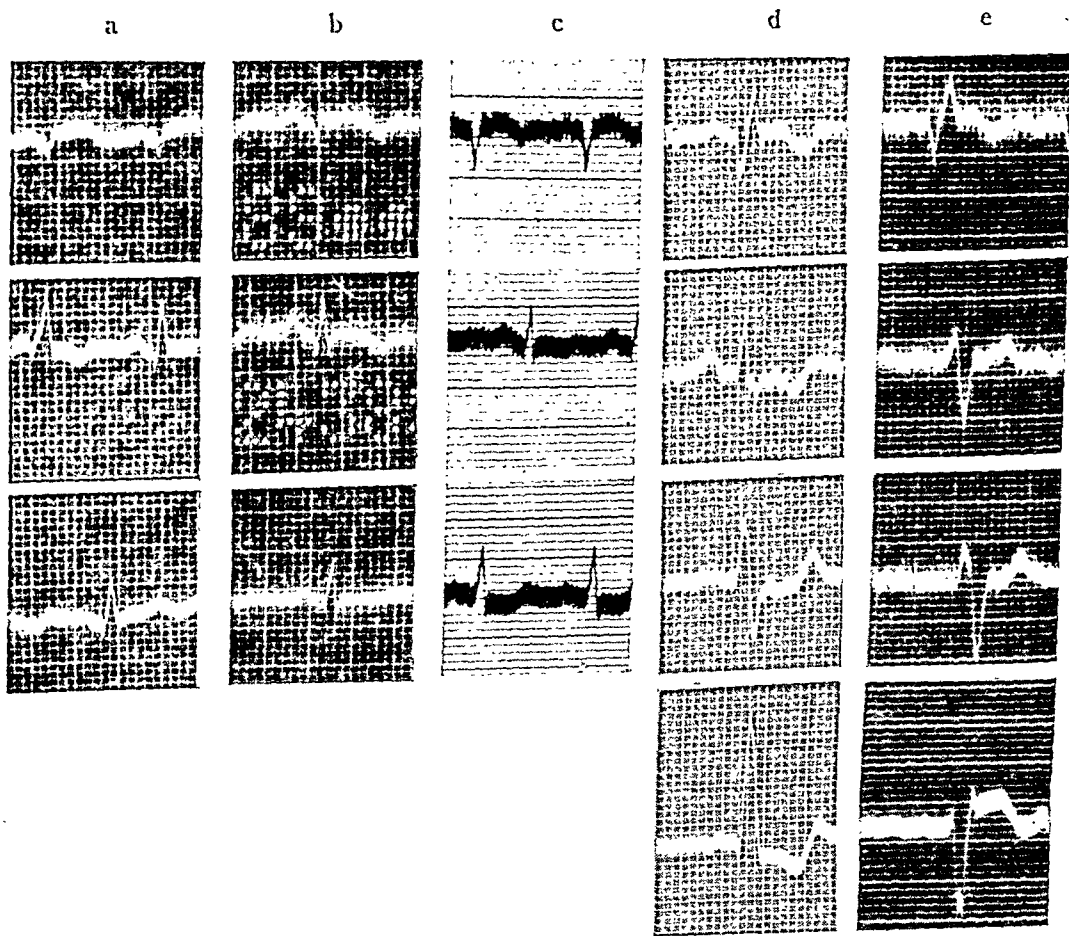


FIG. 1. Electrocardiograms.

- 1 a. (9/25/31)  $RT_1$  elevation,  
 $Q_1Q_2$  present.
- 1 b. (10/30/31)  $T_1T_2$  inverted,  
 $Q_1Q_2$  present.
- 1 c. (2/29/32) Right axis deviation,  
 $T_1T_2$  inverted,  $RT_2$  depressed.
- 1 d. (10/5/37) Right bundle branch block  
(QRS 0.12 second).  
Old Lead IV.
- 1 e. (8/26/41) Bundle branch block.  
Added auricular fibrillation.

presence of a ventricular bulge. Ten days later this prominence had increased in size. The electrocardiographic changes were progressive (figure 1 b).

The patient was discharged improved on November 29, 1931, but was rehospitalized nine days later for bilateral bronchopneumonia and congestive heart failure. The course was stormy, requiring a phlebotomy, digitalization and a two and a half week period in an oxygen tent, but thereafter improvement was steady. The electrocardiogram showed no significant change. Radiographic examination revealed an increase in the size of the ventricular bulge which on fluoroscopy was seen to expand outwardly in systole while the rest of the ventricle contracted. The aneurysmal bulge was prominent in the right anterior oblique position, but was not visualized in the left

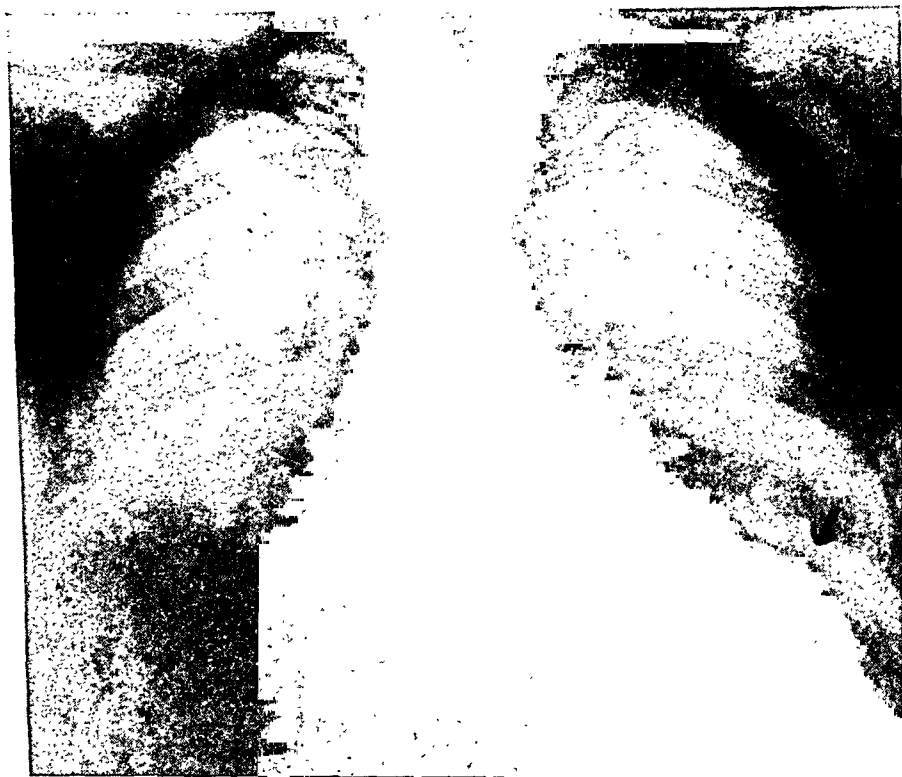


FIG. 2. (2/2/32) Roentgenogram four months after the onset of cardiac infarction. A localized ventricular bulge is noted in the left ventricular contour. The pulmonary changes in the right lower lung field were attributed to pulmonary infarction associated with a slight hydrothorax.

anterior oblique. The impression at this time was that the inflow tract of the left ventricle was not involved in the aneurysmal process.

On January 27, 1932 he was admitted to Montefiore Hospital. Congestive failure was present. The enlarged heart and the disproportion between the forceful apical pulsations and the faint heart sounds suggested the diagnosis of ventricular aneurysm. The decholin circulation time was 21.5 seconds. Therapy consisted of salt-poor, fluid-restricted diet, digitalis, salyrgan, and right thoracenteses.

On fluoroscopy the left ventricle was greatly enlarged and its pulsations were poor. An angular bulge was noted in its upper middle contour. The left auricle was enlarged horizontally. Moderate enlargement of both the outflow and inflow tracts of the right ventricle was present. Four months later there was further enlargement of the left ventricle, especially in the region of the aneurysmal bulge. In

the left anterior oblique view an area of increased density was seen to occupy most of the posterior left ventricular contour. This increased density was believed to be due to an organized thrombus within the aneurysmal bulge.

Four months after admission to Montefiore he was discharged as markedly improved. For the next nine years he was observed frequently in the adult cardiac clinic. Throughout this period he continued his occupation as a machine operator, working 35 hours a week, and traveling to and from his job daily by street car and subway. During the first year salyrgan was given approximately once a month, but thereafter it was no longer necessary since there were no signs of congestive failure.



FIG. 3. Right anterior oblique view. The ventricular bulge is noted to project anteriorly and upward.

There were other admissions to the hospital, once for gingival abscesses and twice for treatment of a right renal colic. Except for mild dyspnea he was essentially asymptomatic while he was taking digitalis and ammonium chloride. Beginning in April 1941 he developed severe dyspnea, orthopnea, hepatic enlargement, and edema up to the knees, which became increasingly more difficult to control.

On August 25, 1941 he was admitted to the hospital for the fifth time because of congestive failure. The blood pressure was 102 mm. Hg systolic and 80 mm. diastolic. There were two separate, synchronous, forceful apical pulsations, one in the fourth left interspace 10 cm. from the midsternal line and the other in the fifth, 11 cm. from the midsternal line. The left border was 1 cm. beyond both of these pulsations. The heart sounds were of poor quality and out of proportion to the intensity of the pulsa-

tions. The rate was 60 per minute with frequent ventricular premature contractions. An apical systolic blow was present.

The fluid accumulation responded readily to the usual cardiac régime of bed rest, restriction of fluid and salt, and intravenous mercurials so that after a week he felt quite well and was permitted to walk about. On September 8, 1941 he developed an acute severe colicky pain in the right upper quadrant just above and to the right of the umbilicus. The liver enlarged progressively; sibilant râles were heard throughout the lungs. He responded well to morphine, oxygen and intravenous aminophyllin; the lungs cleared so that by the following day oxygen was no longer necessary. On

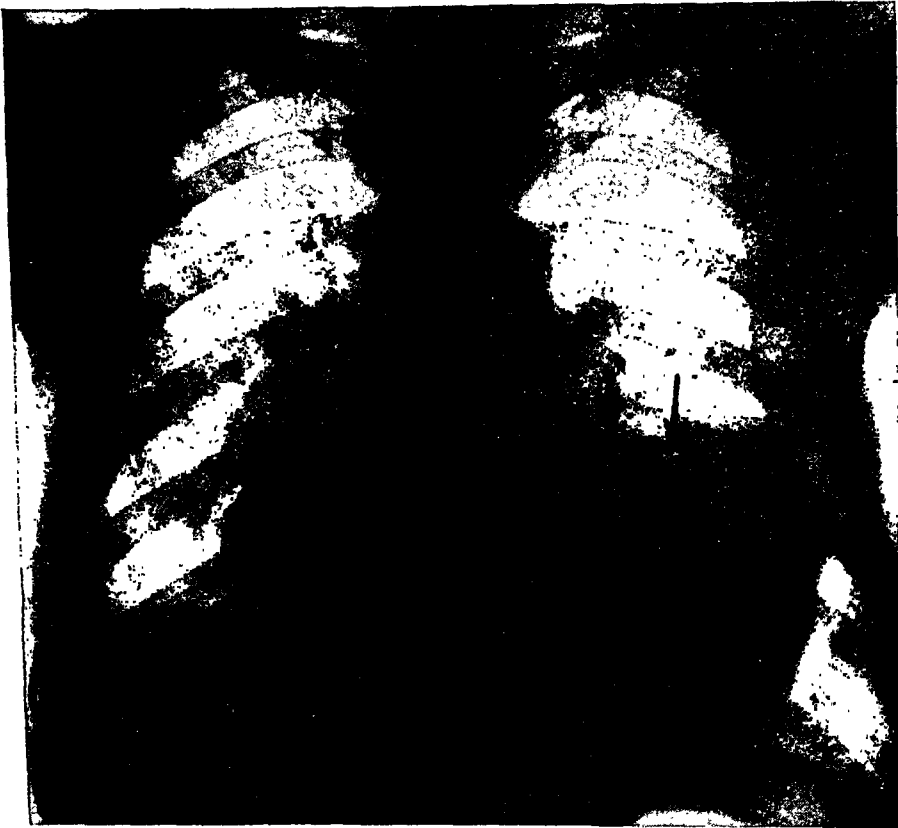


FIG. 4. Same heart 10 years after the onset of cardiac infarction. Calcified plaques were noted in the left lower cardiac contour; a double row of calcification was seen in the original roentgenogram (site indicated by arrows) within the coronary arteries.

September 10 he complained of paraumbilical pain, shortly thereafter became cold, clammy and pulseless, and died 45 minutes later.

Throughout the nine years of observation at Montefiore Hospital radiographic examination demonstrated progressive enlargement of the ventricular aneurysm. The characteristics are described in the captions of figures 2, 3, 4. The electrocardiographic findings are also described with their respective figures (figure 1).

The autopsy diagnosis was: Hypertrophy and dilatation of the heart. Arteriosclerosis of the aorta. Extensive arteriosclerosis of the coronary arteries with old occlusion of the left anterior descending and right main coronary arteries, and marked narrowing of the circumflex branch of the left coronary artery. Old healed infarct of the septum, anterior and posterior walls of the left ventricle with aneurysmal dilatation and mural thrombus formation involving the anterior, lateral, and posterior



walls of this chamber. Obliterative pericarditis. Old healed infarcts of the spleen and kidneys. Chronic passive congestion of the viscera. Pleural effusion, bilateral. Congestion and edema of the lungs.

The heart weighed 869 grams. The pericardial sac was completely obliterated by



FIG. 5. Photograph of unopened anatomical specimen showing the ventricular bulge.

fibrous adhesions. The left ventricle measured 20 to 22 mm. in thickness above the infarcted area; the right ventricle was 4 mm. thick at the apex and 6 mm. thick at the base. The left ventricular wall at the aneurysmal site measured 1 to 3 mm. in thickness and consisted of very dense grayish-brown tissue with little recognizable muscle. It was of the consistency of cartilage and scattered throughout were calcific deposits.

The aneurysmal bulge involved most of the anterior wall of the left ventricle, the greater part of the interventricular septum, and slightly less than the lower half of the posterior wall, mostly laterally. It measured 10 by 8 by 7 cm. and was filled with firm lamellated brown and brownish-red thrombus.

The myocardium of the uninvolved portion of the left ventricle was thick, firm and reddish-brown, with gray fibrous streaks where it joined the infarcted area. The papillary muscles were hypertrophied and contained similar gray fibrous streaks. The



FIG. 6. Roentgenogram of figure 5 indicating the extent of calcification within the left ventricular wall, the organized thrombus, and in the left descending coronary artery.

entire left ventricular chamber was markedly dilated. The right ventricle and both auricles were moderately hypertrophied and dilated. Except for a few atherosclerotic plaques on the mitral and aortic leaflets, all valve rings were normal but moderately dilated. The interventricular septum bulged into the right ventricle especially posteriorly, accentuating greatly the anteroposterior inclination from left to right.

The coronary arteries showed a marked degree of arteriosclerosis with thickening of the walls, atheromata, calcification and extensive occlusion of the two major vessels. The ostium of the left coronary was widely patent but about 1 cm. below, a

point of marked atherosclerotic narrowing was present. The lumen of the anterior descending ramus was completely occluded by firm, gray, fibrous tissue extending for a distance of 2 cm. Save for a small portion of narrowing, the rest of the lumen was occluded down to the infarcted area, where the artery became a calcified and partly ossified solid rod. The larger branches of the anterior descending ramus also revealed marked arteriosclerotic narrowing. There were many sites of moderate to marked narrowing in the left circumflex branch. These were due to plaques which at times reduced the lumen to a mere eccentric slit. The ostium of the right coronary artery was narrowed for about 1 cm. to a diameter of 1.5 mm. by yellow and gray atherosclerotic plaques. The lumen was completely occluded but had been recanalized for a distance of 2 to 3 cm. beyond this area and thereafter was widely patent, with only moderate atherosclerotic narrowing.

Microscopically, the left ventricle adjacent to the infarct showed a fibrous, thickened epicardium, marked hypertrophy of the muscle fibers, and large areas of replacement fibrosis. The right ventricle was similarly though less extensively affected. The wall of the left ventricular aneurysm consisted of dense fibrous tissue, partly hyalinized with few tissue cells and blood vessels. A section through the left coronary artery showed the lumen to be completely occluded by poorly vascularized cellular and fibrous tissue. The wall of this artery was the seat of severe arteriosclerosis with extensive destruction of the media and its replacement by hyalinized fibrous tissue containing plaques of calcium.

#### DISCUSSION

From the first reported case (Olaus Barrich, 1676<sup>1</sup>) through those of Galeati<sup>2</sup> and John Hunter<sup>3</sup> in 1757, to the time of Sternberg,<sup>4</sup> aneurysm of the heart existed as a pathological entity. The latter is credited with the first intravital diagnosis of this condition. Since then numerous papers have appeared describing the method of radiographic and clinical recognition. In the few follow-up studies presented, longevity following the establishment of the diagnosis of ventricular aneurysm has not been a significant factor, and in the majority of reports, death ensued shortly after the diagnosis had been made. Although in a previous study (Gross and Schwedel<sup>5</sup>), based on postmortem analysis, it was shown that ventricular aneurysm does not alter the clinical course, which depends on the underlying hypertensive or arteriosclerotic heart disease, a 10-year survival period is most unusual following this complication of acute coronary occlusion with myocardial infarction. Of the seven who died in Parkinson, Bedford, and Thomson's<sup>6</sup> series of 15 cases, the degree of longevity after diagnosis of ventricular aneurysm ranged from one week to 30 months, averaging 10 months, whereas several others, two, four, and five years after, were able to pursue a comparatively active life. In Dressler and Pfeiffer's<sup>7</sup> 10 reported cases, the duration of life following recognition of the aneurysm varied from three weeks to seven years, those who achieved the upper ranges having been able to carry on normal daily activity or even strenuous physical effort. Ball<sup>8</sup> has reported a patient able to work without marked evidence of cardiac or circulatory failure five and one half years later, and Fulton's<sup>9</sup> two patients lived one and a half and five years after the probable time of aneurysm formation. Berk<sup>10</sup> has followed two cases that have lived for nine years and two for seven years after the initial coronary occlusion or after the development of characteristic radiographic findings of ventricular aneurysm.

So far as could be determined, the case reported here is the longest on record.

In addition to the remarkable longevity, the patient was observed over this 10 year period, and all of the clinical, electrocardiographic, and radiographic findings are available forming a composite picture of almost all such data described in the literature. Although no electrocardiographic tracing typical of ventricular aneurysm exists, Sigler and Schneider<sup>11</sup> reported a pattern of significant corroborative value, i.e., low voltage with the major ventricular deflection being directed upwards in Lead I and downwards in Leads II and III. This is the so-called "aBB pattern" previously described by Winternitz<sup>12</sup> in through and through apical infarction. Gross and Schwedel<sup>5</sup> mention the comparative frequency of progressive deviation of the electrical axis to the right in ventricular aneurysms. Eliaser and Konigsberg<sup>13</sup> have demonstrated an electrocardiographic syndrome present in 27.3 per cent of the  $S_1$  type—a downward major deflection and an inverted T-wave in Lead I, and an upright QRS complex in the third lead, giving a right axis deviation; 36.4 per cent presented a pattern similar to that described by Sigler and Schneider, with or without low amplitude of the ventricular complex in the first lead ( $S_2$ ,  $S_3$  type); and 18.2 per cent displayed an electrocardiogram of left bundle branch block.

Whether these changes were due to the progressive myocardial changes of an enlarging aneurysm with its organizing and calcifying thrombus, or to changes in conductivity of tissues in contact with the external surface of the heart, or to rotation of the heart around its longitudinal axis cannot be stated.

#### SUMMARY

A case of ventricular aneurysm is reported, unique both because of a 10 year survival period and the demonstration of almost all the known clinical and laboratory phenomena associated with this condition.

#### BIBLIOGRAPHY

1. BARRICH, O., cited by STEEL, D.: The roentgen diagnosis of cardiac aneurysm, *Jr. Am. Med. Assoc.*, 1934, cii, 432.
2. GALEATI, D. G.: Comment, BARRON, 1757, iv, 26. (cited by LEGG, J. W.: Some account of cardiac aneurysms, 1884, London).
3. HUNTER, J.: An account of the dissection of morbid bodys, 1757, No. xxxii, p. 30-32.
4. STERNBERG, M.: Das chronische partielle Herz-aneurysma, 1914, F. Deuticke, Leipzig.
5. GROSS, H., and SCHWEDEL, J. B.: The clinical course in ventricular aneurysm, *New York State Jr. Med.*, 1941, xli, 488.
6. PARKINSON, J., BEDFORD, D. E., and THOMSON, W. A. R.: Cardiac aneurysm, *Quart. Jr. Med.*, 1938, vii, 455.
7. DRESSLER, W., and PFEIFFER, R.: Cardiac aneurysm: A report of 10 cases, *ANN. INT. MED.*, 1940, xiv, 100.
8. BALL, D.: Aneurysm of the heart, *Am. Heart Jr.*, 1938, xvi, 203.
9. FULTON, M. A.: Aneurysm of the ventricle of the heart, *Jr. Am. Med. Assoc.*, 1941, cxvi, 115.
10. BERK, L. H.: Personal communication to the authors.
11. SIGLER, L. H., and SCHNEIDER, J. J.: Diagnosis of cardiac aneurysms with report of two cases, *ANN. INT. MED.*, 1935, viii, 1033.
12. WINTERNITZ, M.: The initial complex of the electrocardiogram after infarction of the human heart, *Am. Heart Jr.*, 1933, ix, 616.
13. ELIASER, M., and KONIGSBERG, J.: Electrocardiographic findings in cases of ventricular aneurysm, *Arch. Int. Med.*, 1939, lxiv, 493.

## EDITORIAL

### PSYCHOSOMATIC MEDICINE

WHAT is this psychosomatic medicine about which we have been hearing so much in recent years? Is it a brand new medical art or merely a new name for an old art? Surely the latter explanation comes far closer to the truth, for what medical man from the country doctor to the urban ultra-specialist has not on numerous occasions employed the tools of psychosomatic medicine? The success that a given physician may hope to attain in employing these tools will be directly proportional to his interest in psychosomatic concepts, the time that he is willing to devote to the elucidation of such factors, and the amount of common sense with which he is endowed.

As Hinsie succinctly expresses it in the introductory chapter to a current symposium<sup>1</sup> on psychosomatic medicine: "Living as a human being often takes more energy than the daily tasks that gain us a livelihood. It is easier to get settled in an occupation than it is to adjust ourselves to the personal side of people. It is one of the peculiarities of man that when his energies cannot be essentially externalized, they dam up within him, within his mind or body or both. This persistent damming up leads to tension and symptoms. When the symptoms are in the mental sphere, they give rise to special names, such as psychosis and psychoneurosis. When the tensions of living localize themselves in different parts of the body, it appears that the organic part involved is the seat of the trouble, that is, the organ appears "diseased." In a broad sense of the word it is diseased, it is deprived of ease, it is disordered functionally, but the trouble stems from unhappy adjustment to life and not from such organic sources as bacteria, injury, etc. . . . The term pathology is enlarged to include abnormal emotions. Hence, it is said that the organ shows psychopathology."

Psychosomatic complaints manifest themselves in almost any organ or system of the body. The recognition of the true nature of such complaints may require an extensive diagnostic survey in order to rule out true organic disease and thereby serve as a basis for reassurance of the patient. Let us take, for example, the commonplace complaint of *headache*. The busy practitioner may be tempted to pass the complaint off lightly with the advice to take aspirin or some other highly advertised headache remedy. Such preparations will usually afford temporary relief, but the patient will continue to have his headaches. He often becomes convinced that he has sinus trouble or that his eyes are to blame. Therefore, careful examination of the eyes, including refraction and ophthalmoscopic examination, and nose and throat survey, supplemented with sinus roentgenograms, are essential before such local causes can be eliminated to the satisfaction of the patient. In addition

<sup>1</sup> Symposium on psychosomatic medicine, Med. Clin. North Am., W. B. Saunders Co., 1944, p. 525.

to general physical examination, blood count, and urinalysis, a careful neurologic examination, serologic test for syphilis, roentgenogram of the skull and, at times, even ventriculography must be resorted to in order to rule out an organic intracranial basis for the headaches. The characteristics of the headaches—throbbing, squeezing, constricting, drawing, pressing, splitting, localized or generalized—and the circumstances under which they occur will provide the physician with valuable clues as to their true nature. Reinforced with the battery of negative organic findings obtained from the various examinations just enumerated, he is in a more secure position to reassure the patient that his fears or suspicions of a serious organic basis are unjustified and to explore the possibilities of a functional or psychogenic background. It may turn out that the victim is unhappy at his work, working under too much pressure from his boss, burdened with financial or domestic worries (such as a nagging wife or an interfering mother-in-law), or he may be too meticulous in his way of living, constantly upset by trivialities. It is amazing how rapidly and completely tension headaches may clear up following a change in job, improvement in the domestic situation, or adoption of a less perfectionistic outlook on life. Although migraine headaches and so-called "histamine headaches" have been sidetracked through general consent into special categories of their own, the writer is inclined to regard these headaches also as localized vascular outlets (either vasoconstrictory or vasodilatory) for pent-up emotional tension with a definite hereditary pattern in the migraine type.

An equally fruitful field for the psychosomatic approach is to be found in the everyday complaint of *low backache*, especially common in women. And here once more, an extensive diagnostic survey is indicated before we are warranted in concluding that the backache is functional in origin. A detailed history of the development and characteristics of the major complaint, general physical examination, and such special studies as pelvic examination by a competent gynecologist, orthopedic consultation with roentgenograms of the lower spine, and at times cystoscopic study, lumbar puncture, and barium enema should be obtained in order to rule out a local organic cause for the backache. If these special examinations fail to reveal any significant physical abnormality, the physician is justified in suspecting a functional basis for the patient's complaint. It may turn out that the backache is serving as a subconscious (or conscious!) escape from the ardors of housework, the unpleasant prospect of entertaining, or the overzealous onslaughts of Hertzler's "tomcat" husband. Sexual maladjustment is so frequently at the root of chronic backache that it should invariably be considered in cases for which no organic cause can be detected.

Headache and low backache have been selected as two of the most frequently encountered psychosomatic complaints. One could mention many others, among the more common of which are the variegated symptoms of spasticity of the gastrointestinal tract—abdominal pain, vomiting, heartburn,

and diarrhea—which must be differentiated from such organic disorders as ulcer, gall-bladder disease, appendicitis, ileo-colitis, and carcinoma; anxiety attacks with palpitation, dyspnea, and precordial pain to be distinguished from organic heart disease, paroxysmal nocturnal dyspnea, and angina pectoris; psychogenic arthralgias and neuralgias so difficult to separate clinically from true arthritides or neuritides; and functional urinary frequency, hesitancy, and urgency simulating cystitis or other organic disturbances of the genito-urinary tract. The differential diagnosis in all of these conditions rests upon a careful survey of the area involved, followed by an investigation of the personality make-up of the individual concerned, his background, ambitions, frustrations, and tensions; his domestic, religious, and economic problems; his working conditions; his ability to relax and to indulge in healthful recreation. The positive demonstration of a basis for such a psychoneurotic reaction is just as essential for diagnosis as the exclusion of gross organic disease. The trained psychiatrist can be of inestimable assistance to the practitioner or internist in working out the more complicated problems, but there are just not enough psychiatrists to go around, so that the great majority of the psychosomatically afflicted must remain in the lap of their personal physician to “kill or cure” as he sees fit! Many doctors fail to realize how much serious damage they have wrought upon the patient’s psyche by such careless remarks as, “You are on the verge of a stroke” or “I cannot be certain whether it is cancer or not.” Iatrogenic symptoms may comprise 90 per cent or better of some patients’ complaints and may prove most difficult to eradicate.

One note of warning is in order, namely the danger of jumping to the conclusion that a patient’s complaints are purely psychogenic and, therefore, failing to carry out procedures essential to differential diagnosis. The psychiatrist, himself, is perhaps more likely to slip into this error than the general clinician who is constantly seeing organic disease as well as functional disorders. Granting that there may be much important psychogenic material in victims of peptic ulcer, ulcerative colitis, asthma, etc., still none but the most analytical-minded of psychiatrists would attempt to treat such patients by psychotherapeutic measures alone.

The importance of the recent emphasis upon psychosomatic medicine must be obvious at a time when human beings everywhere are being subjected to stresses and strains, in both military and civilian life, such as they have never encountered before. The promulgators are to be congratulated upon the timeliness of their efforts with the publication of texts, symposia, and a journal devoted exclusively to psychosomatic medicine. It behooves every physician and surgeon, no matter how broad or narrow his chosen field may be, to familiarize himself with the basic concepts of this science. The therapeutic triumphs that he will gain thereby may far outweigh the victories he wins with drug or scalpel!

W. H. B.

## REVIEWS

*Clinical Pediatrics*. Oxford Medical Outline Series. By I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D. 393 pages; 14.5 × 22 cm. Oxford University Press, New York, N. Y. 1943. Price, \$2.00.

This volume follows the trend begun several years ago of presenting subjects in outline form.

The lack of coherence and the close resemblance to a student's notebook give the reviewed book a very limited usage. It is possibly suitable for students preparing for examination and maybe for general practitioners who wish to find information in haste.

The book falls far short of the author's purpose as expressed in the preface to emphasize the determining features of pediatric problems.

J. E. B.

*Applied Dietetics*. 2nd Edition. By FRANCES STERN. 265 pages; 26 × 18 cm. Williams and Wilkins Company, Baltimore. 1944. Price, \$4.00.

This second edition of *Applied Dietetics* is a very concisely put together book. It combines the latest in nutrition research with explanations of therapeutic diets that a beginner can understand. It is a compilation of information of use to the nutritionist, dietitian, doctor, social worker and the like. The book is arranged in four sections, the first devoted to the construction of the therapeutic diet as a deviation from the normal diet, the second is a series of tables to simplify the computation of the diet, the third is devoted to dietary outlines for the treatment of most common diseases, and the fourth part to typical diets and menus.

Miss Stern's development of the therapeutic diet from the normal diet in relation to the body needs and capabilities is an excellent introduction for the student who is interested in seeing why such special diets are needed. The emphasis is on the patient as an individual. It explains the methods of gaining patient coöperation and how to explain a therapeutic diet as a modification of the normal.

The second section of the book is entirely in tabular form and to gain the maximum advantage from it would take considerable time. However, I believe that if the reader were thoroughly familiar with the tables, the time saving factor in computing therapeutic diets to meet nutrition standards would be of great advantage.

Complete dietary outlines which consist of the dietary treatment of 23 diseases and abnormal conditions make up the third section. Each outline considers the body part affected, the normal and pathological physiology, the dietary treatment and contributing factors, food for the day, the reason for the selection of foods used, and the education of the patient as to his condition and dietary treatment.

The fourth section is the practical application of the third section which suggests meal plans and evaluates these meal plans for the necessary food constituents.

To understand Miss Stern's book requires that the reader be well educated in physiology and nutrition. It will be of chief value for reference material for those interested in dietary treatment of diseases and of much value in instructing the patient as to his own particular needs. The first section of the book is much simpler to understand than the remainder and might well be used as the basis for instructing patients who do not have all the scientific background of professional people who are chiefly interested in the scientific facts which make up the last three sections.

H. B.



## BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Clinical Evaluation of the Rehabilitation of the Tuberculous.* By LOUIS E. SILTZBACH, M.D. 70 pages; 23.5 × 15.5 cm. 1944. National Tuberculosis Association, 1790 Broadway, New York 19, N. Y. Price, \$1.00 cloth-bound; \$.50 paper cover.
- Notes on Nursing by a Nurse.* By SARAH CORRY, R.N. 144 pages; 19.5 × 13 cm. 1944. D. Appleton-Century Co., 35 W. 32nd St., N. Y., N. Y. Price, \$1.50.
- Intracranial Arterial Aneurysms.* By WALTER E. DANDY. 147 pages; 24 × 16 cm. 1944. Comstock Publishing Company, Inc., 124 Roberts Place, Ithaca, N. Y. Price, \$2.50.
- Manual of Human Protozoa.* By RICHARD R. KUDO, D.Sc. 125 pages; 20 × 13 cm. 1944. Charles C. Thomas, Springfield, Ill. Price, \$2.00.
- Practical Malaria Control. A Handbook for Field Workers.* By E. M. GUNTHER, M.D., B.S., D.T.M. (Sydney). Foreword by PROF. HARVEY SUTTON, O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R. San.I. 91 pages; 20 × 13.5 cm. 1944. Philosophical Library, Inc., 15 E. 40th St., N. Y., N. Y. Price, \$2.50.
- The Treatment of Peptic Ulcer.* By GEORGE J. HEUER, M.D. Assisted by CRANSTON HOLMAN, M.D., and WILLIAM A. COOPER, M.D. 118 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, \$3.00.
- Radiation and Climatic Therapy of Chronic Pulmonary Diseases.* Edited by EDGAR MAYER, M.D., F.A.C.P., F.A.C.C.P., with the collaboration of 22 other contributors. 393 pages; 23.5 × 16 cm. 1944. Williams & Wilkins Company, Baltimore. Price, \$5.00.
- The Management of Neurosyphilis.* By BERNHARD DATTFNER, M.D., Jur.D., with the collaboration of EVAN W. THOMAS, M.D., and GERTRUDE WEXLER, M.D. Foreword by JOSEPH EARLE MOORE, M.D. 398 pages; 23.5 × 16 cm. 1944. Grune & Stratton, Inc., New York, N. Y. 1944. Price, \$5.50.
- Intravenous Anesthesia.* By R. CHARLES ADAMS, M.D., C.M., M.S.(Anes.). 663 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, \$12.00.
- The Principles and Practice of Tropical Medicine.* Part I—Dealing with nearly all the major tropical diseases. By L. EVERARD NAPIER, C.I.E., F.R.C.P. 522 pages; 25.5 × 17 cm. 1943. Thacker, Spink & Co., Ltd., Calcutta; W. Thacker & Co., London. Price, 25 rupees.
- The Use of Penicillin in Treating War Wounds.* Instructions prepared by the Penicillin Clinical Trials Committee. Medical Research Council War Memorandum No. 12. 16 pages; 24.5 × 15.5 cm. 1944. His Majesty's Stationery Office, York House, Kingsway, London, W. C. 2. Price, \$1.0. (Code No. 45-9999.)
- The Control of Cross Infection in Hospitals.* Memorandum prepared for the Committee on Preventive Medicine of the Medical Research Council by the Subcommittee on Cross Infection in Hospital Wards. Medical Research Council War Memorandum No. 11. 34 pages; 24.5 × 15.5 cm. 1944. His Majesty's

Stationery Office, York House, Kingsway, London, W. C. 2. Price, \$.15. (Code No. 45-9-11.)

*Polinosis.* By LEOPOLDO HERRAIZ BALLESTERO (Doctor en Medicina) and JUAN VICTOR MONTICELLI (Doctor en ciencias naturales). 227 pages; 23 × 16 cm. 1943. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

*Anemopolinologia Aplicada.* By MIGUEL AGUSTIN SOLARI. 54 pages; 26.5 × 18 cm. 1942. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

*Sueroterapia por Nebulizacion.* Tesis de Doctorado. By ANDRES MARTINEZ MARCHETTI. 47 pages; 26.5 × 18 cm. 1942. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

*Valor Diagnostico de Ciertos Sintomas de Alergia Menor.* Estudio Estadístico de las Manifestaciones Sintomáticas de la Alergia en la Zona de la Capital Federal. By BENIGNO R. GARAT. 44 pages; 27 × 18 cm. 1943. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

## COLLEGE NEWS NOTES

### ADDITIONAL A.C.P. MEMBERS IN THE ARMED FORCES

Previously reported in the News Notes section of this journal were the names of 1,699 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,701.

John A. Baird  
Albert M. Eaddy

Notice has been received that Lt. Comdr. Roland N. Klemmer, (MC), USNR, F.A.C.P., of Lancaster, Pa., died in the South Pacific on May 9, 1944, of a heart ailment.

Major Erle B. Craven, Jr., (MC), AUS, was retired to inactive service on December 14, 1943, and has resumed the practice of medicine at Lexington, N. C., and teaching at Duke University.

Captain Louis Friedfeld, (MC), AUS—honorably discharged, April 29, 1944.

---

### NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Dr. Thomas T. Holt, Wichita, Kans.  
Dr. Thomas Donald Cunningham, Denver, Colo.  
Dr. Henry K. Speed, Sayre, Okla.

---

### GIFTS TO THE COLLEGE LIBRARY

The following gifts are graciously accepted:

#### *Books*

Dr. Louis E. Siltzbach (Associate), New York, N. Y.—“Clinical Evaluation of the Rehabilitation of the Tuberculous.”

#### *Reprints*

Lewis H. Bronstein (Associate), Captain, (MC), AUS—2 reprints.  
Abraham G. Cohen (Associate), Major, (MC), AUS—1 reprint.  
Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn.—1 reprint.  
Ellis H. Hudson, F.A.C.P., Commander, (MC), USNR—1 reprint.  
Alfred L. Kruger (Associate), Captain, (MC), AUS—1 reprint.  
Dr. Robert C. Moehlig, F.A.C.P., Detroit, Mich.—1 reprint.  
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—1 reprint.  
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—1 reprint.  
George F. Schmitt, Jr., F.A.C.P., Lieutenant, (MC), USNR—1 reprint.  
Maurice A. Schnitker, F.A.C.P., Major, (MC), AUS—2 reprints.  
Dr. Maurice S. Segal, F.A.C.P., Boston, Mass.—2 reprints.  
Dr. Isaac J. Silverman, F.A.C.P., Washington, D. C.—1 reprint.  
Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.—5 reprints.

## A.C.P. MEMBERS IN MISSISSIPPI HELD LUNCHEON MEETING

Under the Governorship of Dr. John G. Archer, F.A.C.P., the annual luncheon of the Mississippi members of the American College of Physicians was held May 9, at the Robert E. Lee Hotel, Jackson, Miss., during the annual meeting of the Mississippi State Medical Association. Dr. William C. Chaney, F.A.C.P., Governor of the College for Tennessee, gave an address on the Wagner-Murray-Dingell Bill, and Major George M. Knowles, (MC), AUS, F.A.C.P., presented a paper on Arthritis. There was a round-table discussion after each address. The meeting was most successful and the attendance good.

---

## CAPTAIN RICHARD A. KERN, F.A.C.P., RECEIVED CITATION

Captain Richard A. Kern, (MC), USNR, formerly of Philadelphia, received the following citation from Admiral W. F. Halsey for services as set forth below:

"For meritorious and efficient performance of duty while serving as Medical Consultant on the Staff of the Commander South Pacific Area and South Pacific Force during the period from August, 1943, to February, 1944. Captain Kern, in discharging his duties, made his services available to every medical officer in the South Pacific Area, visiting every medical facility many times. He traveled throughout the forward and combat areas, and worked with the medical officers in the front line of combat operations on Bougainville, British Solomon Islands. At all times his objective was to improve the treatment of the sick and wounded, and no undertaking was too great, nor any detail too small, to bring forth his best efforts toward that end. His tireless endeavors, professional ability and devotion to duty were in keeping with the highest traditions of the United States Naval Service."

Captain Kern has been returned to the United States, and is now serving as Chief of Medicine at the United States Naval Hospital, Philadelphia.

---

Major Dickinson Sergeant Pepper, (MC), AUS, F.A.C.P., has been advanced to Chief of Medicine at the McGuire General Hospital, Richmond, Va.

---

## WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA ORGANIZES POSTGRADUATE COURSES IN PRE-CLINICAL SCIENCES

The Woman's Medical College of Pennsylvania at Philadelphia organized in the autumn of 1943 a postgraduate course for the review of the pre-clinical sciences, the course being given throughout the fall, winter, and spring of 1943 and 1944. The faculty was made up very largely from the faculty of the Medical College. The course was attended by a group ranging from 25 to 45 throughout the year, many of them taking advantage of the course to prepare for the examinations of the American Board of Internal Medicine. Physiology and physiological chemistry were among the most popular subjects.

The review course in the pre-clinical subjects will not be repeated until 1946, but the same group will continue in the autumn of 1944 in review work in clinical subjects, such as parasitology, electrocardiography, roentgenology and tuberculosis.

Dr. William G. Leaman, Jr., F.A.C.P., Professor of Medicine, Woman's Medical College, has largely directed the organization of the course.

---

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., and Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., are Chairman and member, respectively, of the Scientific Advisory Committee of the Baruch Committee on Physical Medicine, recently an-

nounced in these pages. The offices of the Committee, which was created by a recent gift of \$1,100,000.00 from Mr. Bernard M. Baruch, are at 597 Madison Ave., New York City. Miss Grace Keef, Executive Secretary, will supply to those asking for it, copies of the report on which Mr. Baruch based his donation.

Dr. Charles M. Griffith, F.A.C.P., Washington, D. C., Medical Director of the United States Veterans Administration, Lt. Col. Howard A. Rusk, (MC), AUS, F.A.C.P., Chief of the Convalescent Division, Office of the Air Surgeon, War Department, and Captain Howard Montgomery, (MC), USN, F.A.C.P., Chief of Rehabilitation, Bureau of Medicine and Surgery, Navy Department, Washington, D. C., have been appointed members of the Committee on War and Post-War Physical Rehabilitation and Reconditioning.

---

Colonel Charles F. Craig, F.A.C.P., Emeritus Professor of Tropical Medicine, Tulane University of Louisiana, recently received the Theobald Smith Gold Medal of the George Washington University School of Medicine, in recognition of his contributions in the field of Tropical Medicine.

---

Blakiston Company, medical publishers, Philadelphia, has recently been acquired by Doubleday-Doran & Company, Inc. The Blakiston Company, however, will continue its present publication business under its original name and under the direction of its former President, Mr. Horace G. White, and the entire personnel.

---

Lt. Comdr. Harold J. Harris, (MC), USNR, F.A.C.P., addressed the New York Society for Clinical Ophthalmology, May 1, 1944, on the subject of brucellosis in ophthalmology.

---

Brigadier General James Stevens Simmons, (MC), USA, F.A.C.P., Chief of the Preventive Medicine Service, Office of the Surgeon General, U. S. Army, has been elected a member of the Council on Industrial Health of the American Medical Association.

On May 17, at the invitation of the Cuban Government and Dr. Alberto Recio, Minister of Health, Brigadier General Simmons visited Havana and took part in the dedication of the new National Institute of Health. In the course of the ceremonies, President Batista decorated General Simmons with the Medal of the Carlos J. Finlay National Order of Merit in the grade of Gran Oficial. The President also transmitted by General Simmons to Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, a certificate conferring the Carlos J. Finlay Order of Merit in the grade of Gran Cruz on the former American Yellow Fever Commission for its fundamental experimental work in Cuba on the etiology and transmission of yellow fever under the leadership of Major Walter Reed. The certificate will be preserved in the Army Medical Library in Washington.

---

Dr. Edward B. Krumbhaar, F.A.C.P., Professor of Pathology, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia, was recently made an Honorary Fellow of the Royal Society of Medicine.

---

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, Calif., has been honored by the Government of Ecuador, by the grant of its exalted decoration, "Al Merito," with the citation, "For distinguished service, for noteworthy and indomitable leadership in the advancement of public health in the Americas."

The Desert Sanatorium of Southern Arizona, Tucson, has discontinued operations after many years of service.

Dr. Roland Davison, F.A.C.P., its Medical Director, has removed to 516 Sutter St., San Francisco 2, Calif., where he will engage in the practice of Internal Medicine.

---

Dr. Floyd L. Rogers, F.A.C.P., Lincoln, was installed as President of the Nebraska State Medical Association at its recent meeting in Omaha, May 1-4.

---

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., has been confirmed as the official appointee of the American College of Physicians in the Division of Medical Sciences, National Research Council, for a three-year term beginning July 1, 1944.

---

Dr. Barnett Greenhouse, F.A.C.P., New Haven, addressed the New Haven Medical Association, May 17, on "Current Trends in Diabetes Mellitus."

---

Announcement was recently received of the advancement of Dr. Francis C. Wood, F.A.C.P., to the rank of Lieutenant Colonel in the Medical Corps of the Army. He is on duty in India.

---

A recent announcement confirmed that the following Fellows of the College attached to the Office of the Surgeon General of the U. S. Army have been promoted in rank, as indicated:

George F. Lull, from Brigadier General to Major General;  
Leon A. Fox, from Colonel to Brigadier General;  
Shelley U. Marietta, from Brigadier General to Major General.

---

Colonel Baldwin L. Keyes, (MC), AUS, F.A.C.P., head of the Jefferson Base Hospital, Philadelphia, Pa., was recently in Philadelphia after service in North Africa.

---

Captain Albert Soiland, (MC), USNR, F.A.C.P., attended the First National Mexican Cancer Congress at Guadalajara, last November, as the authorized delegate from the Bureau of Medicine and Surgery of the U. S. Navy, the American College of Radiology, the American Radium Society, the American Roentgen Ray Society and the American Society for the Control of Cancer.

Captain Soiland was recently notified that he had been appointed Honorary Professor on the faculty of the University of Guadalajara.

---

Dr. Robert S. Berghoff, F.A.C.P., Chicago, who became Acting President of the Illinois State Medical Society last March, following the death of President George Post, was elected President-Elect of the Society at its recent annual meeting in Chicago. He will serve as President-Elect 1944-45, and as President for 1945-46.

---

War, Rehabilitation and Civilian Surgery will be the theme of the Ninth Annual Assembly of the International College of Surgeons at Philadelphia, October 3-5, 1944, with headquarters at the Benjamin Franklin Hotel.

---

The Twelfth Annual Graduate Short Course for Doctors of Medicine, under the auspices of the Graduate School of the University of Florida, the Florida Medical

Association and the Florida State Board of Health, was held at Jacksonville, June 19-24. The course covered the subjects of *pediatrics, obstetrics, gynecology, venereal diseases, medicine, surgery and post-war public health.*

Dr. T. Z. Cason, F.A.C.P., Jacksonville, is the Director of the Postgraduate Committee. Dr. George L. Cook, F.A.C.P., Tampa, and Dr. W. Wellington George, F.A.C.P., West Palm Beach, are members of the Committee.

---

Dr. Raphael Isaacs, F.A.C.P., Chicago, will be the Medical Director of the newly incorporated Hematology Research Foundation. The Foundation has been set up and is being financed by prominent lay persons, and one of the first problems for investigation will be a study of leukemia.

---

Dr. Edward L. Tuohy, F.A.C.P., Duluth, has been elected President of the Minnesota State Medical Association. Dr. Sidney A. Slater, F.A.C.P., Worthington, and Dr. J. Arnold Bargen, F.A.C.P., Rochester, are Vice-Presidents. Dr. Benjamin B. Souster, F.A.C.P., St. Paul, is the Secretary.

---

Dr. Stockton Kimball, F.A.C.P., Associate in Medicine and Pharmacology, and Dr. Lawrence E. Hummel, F.A.C.P., Assistant Dean and Assistant Professor of Medicine, University of Buffalo School of Medicine, have returned from a study of malaria and other tropical diseases in Guatemala.

---

On May 18, Dr. William H. Sebrell, Jr., F.A.C.P., Chief of the Division of Chemotherapy, National Institute of Health, delivered the eighth Harvey Society Lecture of the New York Academy of Medicine, on "The Relation Between Sulfonamide Drugs and Vitamin Deficiencies."

---

The late Dr. Charles W. Burr, F.A.C.P., Emeritus Professor of Mental Diseases, University of Pennsylvania, bequeathed \$200,000.00 to the endowment fund of the University; also left his library of some 19,000 volumes to the University Library.

---

Dr. Joseph McFarland, F.A.C.P., Philadelphia, completed in the early spring a medical lecture tour of Costa Rica and Central America.

---

Dr. Harry C. Schmeisser, F.A.C.P., has resigned as Chief of the Division of Pathology at the University of Tennessee College of Medicine, but he will continue as Professor of Pathology.

---

Dr. Edward L. Turner, F.A.C.P., President of Meharry Medical College, Nashville, Tenn., recently announced a grant by the General Education Board of the Rockefeller Foundation of \$4,000,000 for endowment and \$300,000 for a contingent fund for the above institution.

---

Dr. William C. Chaney, F.A.C.P., Governor of the College for Tennessee, has been elected President-Elect of the Tennessee State Medical Association.

Dr. Ernest R. Zemp, F.A.C.P., Knoxville, was reelected for the twenty-first consecutive year as speaker of the Association's House of Delegates.

The following Fellows of the College gave a radio broadcast in connection with the Doctors at War program of the American Medical Association, as indicated below:

Major General George F. Lull, (MC), USA, Washington, D. C.—June 3, 1944, "Medicine in the Front Lines";  
Dr. James E. Paullin, Atlanta, Ga.—June 11, 1944, "War and the Medical Profession";  
Colonel W. Paul Holbrook, (MC), AUS, Air Surgeon's Office—June 13, 1944, "Rheumatic Fever in the Army Air Forces";  
Lieutenant Colonel Howard A. Rusk, (MC), AUS, Air Surgeon's Office—June 13, 1944, "Convalescent Training Program in Army Air Forces Hospitals";  
Brigadier General James S. Simmons, (MC), USA, Washington, D. C.—June 17, 1944, "Mechanized Dandruff."

---

Dr. Frank J. Milloy, F.A.C.P., Phoenix, was named Secretary of the Arizona State Medical Association at its annual meeting in April.

---

A reading room at St. Luke's Hospital has been dedicated to Dr. Arthur R. Elliott, F.A.C.P., Senior Consulting Physician. Dr. Elliott was responsible for obtaining funds to develop the Library.

---

Dr. Buell H. Van Leuven, F.A.C.P., Traverse City, Michigan, has been appointed Health Director of Chippewa County, and will have his headquarters in Sault Ste. Marie.

---

Dr. Frederick R. Taylor, F.A.C.P., Associate Professor of Clinical Medicine, Bowman Gray School of Medicine, Winston-Salem, has been named Professor of Medical Literature, a newly created position. A course is being devised to give instruction in the relative value of various publications, ethics of medical writing, editing of medical papers, methods of keeping abreast of medical literature, etc.

---

Dr. Edgar McNamee, F.A.C.P., Cleveland, has been made President-Elect of the Ohio State Medical Association.

---

Under the presidency of Dr. Karl J. Henrichsen, F.A.C.P., the American Academy of Tuberculosis Physicians held its annual meeting at Chicago, June 13.

---

Dr. Walter P. Gardner, F.A.C.P., for several years Superintendent of the Anoka State Hospital, recently resigned and will return to private practice in St. Paul, Minn.

---

Dr. Jay C. Davis, F.A.C.P., Minneapolis, has been elected Vice-President of the Minneapolis Academy of Medicine.

---

Dr. Francis E. Harrington, F.A.C.P., Commissioner of Health of Minneapolis, has been elected President of the Minnesota Public Health Association to succeed Dr. Sidney A. Slater, F.A.C.P., Worthington.

---

Dr. Marvin L. Graves, F.A.C.P., Houston, recently received the honorary degree of Doctor of Science, conferred by Baylor University.



Dr. Harry A. Durkin, F.A.C.P., Peoria, has been elected President of the Illinois Heart Association.

---

Dr. Phillip H. Jones, Jr., F.A.C.P., New Orleans, has been elected a Vice-President of the Louisiana State Medical Society.

---

Under the presidency of Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, the American Diabetes Association held its fourth annual meeting at Chicago, June 11.

Colonel Leonard G. Rowntree, (MC), AUS, F.A.C.P., delivered the Banting Memorial Lecture on "Experiences of the Selective Service System with Glycosuria."

---

The Association for the Study of Internal Secretions, under the presidency of Dr. E. Kost Shelton, F.A.C.P., Los Angeles, held its twenty-seventh annual meeting in Chicago, June 12-13. Among the guest speakers were Dr. Maurice Fremont-Smith, F.A.C.P., Boston, and Dr. Willard O. Thompson, F.A.C.P., Chicago.

---

The American Society of Clinical Pathologists held its twenty-third annual meeting in Chicago, June 8-11, under the presidency of Dr. Walter S. Thomas, F.A.C.P., Rochester, N. Y.

Colonel James E. Ash, F.A.C.P., curator of the Army Medical Museum, Washington, D. C., conducted a seminar on "Pathology of Tropical Diseases"; Dr. Israel Davidsohn, F.A.C.P., Chicago, was the moderator.

---

The forty-fifth annual meeting of the American Therapeutic Society was held in Chicago, June 10, under the presidency of Dr. William V. Watson, F.A.C.P., Toronto, Ontario.

---

The forty-sixth annual meeting of the American Gastroenterological Association, under the presidency of Dr. Sara M. Jordan, F.A.C.P., Boston, was held in Chicago, June 12-13. At the annual dinner meeting the Friedenwald Medal was presented to Dr. Anton J. Carlson, F.A.C.P., Emeritus Professor of Physiology at the University of Chicago School of Medicine, and to Dr. Andrew C. Ivy, F.A.C.P., Professor of Physiology and Pharmacology at Northwestern University Medical School.

---

Dr. Thomas Parran, F.A.C.P., Washington, D. C., has received a re-appointment as Surgeon General of the U. S. Public Health Service for another term of four years.

---

Dr. A. Austin Pearre, F.A.C.P., and Dr. John S. Derr, F.A.C.P., both of Frederick, have been elected President and Second Vice-President, respectively, of the Frederick County (Md.) Medical Society.

---

Dr. Cecil O. Patterson, F.A.C.P., and Dr. Merritt B. Whitten, F.A.C.P., have been elected Secretary and Treasurer, respectively, of the Dallas Southern Clinical Society.

Dr. Whitten has also been elected President of the Texas Club of Internists.

---

Dr. Neil D. Buie, F.A.C.P., Marlin, Tex., is Vice-President of the Federation of the State Boards of the United States.

Dr. James Alexander Miller, M.A.C.P., a former President of the American College of Physicians and of the National Tuberculosis Association, was awarded the Trudeau Medal for meritorious achievement in the prevention and treatment of tuberculosis at the last meeting of the National Tuberculosis Association in Chicago, May 10.

Dr. Arthur Grollman, F.A.C.P., heretofore research professor of medicine and associate professor of physiology and pharmacology at the Bowman Gray School of Medicine, Winston-Salem, N. C., has accepted an appointment as professor of experimental medicine at the Southwestern Medical College, Dallas, beginning July 1.

#### NEW EDITION OF DIRECTORY OF MEDICAL SPECIALISTS TO BE PUBLISHED

The third edition of the Directory of Medical Specialists listing names and biographic data of all men certified by the fifteen American Boards is to be published early in 1945. Collection of biographic data of the Diplomates certified since the 1942 edition, and revision of the older listings in that volume, are now going forward rapidly. Diplomates are requested to make prompt return of notices regarding their biographies as soon as possible after receiving the proper forms from the publication office soon to be mailed to them.

#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

*Rhoads General Hospital, Utica, New York*

July 20 Blood and Blood Substitutes: Their Indications and Uses—Dr. Frederick Marty

August 17 Wounds of the Extremities and Their Management—Dr. Roscoe Severance

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller.

*United States Naval Hospital and United States Naval Academy  
Dispensary, Annapolis, Maryland*

July 21 Drug Allergies—Dr. Nathan B. Herman

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole.

*Mayo General Hospital, Galesburg, Illinois*

July 19 Peripheral Vascular Diseases

- a. Diagnosis and Conservative Treatment
- b. Surgical Treatment

*Camp Ellis, Illinois*

July 19 High Blood Pressure

- a. Pathological—Physiological Basis—Conservative Therapy  
Renal Extracts
- b. The Surgical Treatment

*Camp McCoy, Wisconsin*

- July 19    Conditions Affecting Glucose Metabolism  
           a. Endocrine—Pituitary—Thyroid—Adrenal—Pancreatic  
           b. Renal, Alimentary, Hepatic. Diff. Diagnosis and Treatment

*Camp Grant, Illinois*

- July 19    Diseases of the Intestinal Tract  
           a. Regional ileitis, colitis, diverticulitis. Diagnosis and Treatment.  
           b. Dysentery—Amebic and Bacillary  
           c. Malignancies

*Truax Field, Wisconsin*

- July 19    Dermatological Diseases  
           Clinic with Presentation of Cases and Slides. Diagnosis and Treatment.  
           a. The Less Common Venereal Diseases  
               Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid,  
               Yaws—Slides—Diagnosis and Treatment.

*Scott Field, Illinois*

- July 19    Malignancies in the Army Age Group  
           a. Melanomata  
           b. Teratomata  
           c. Lymphoblastomata

*Chanute Field, Rantoul, Illinois*

- July 19    Virus and Rickettsial Diseases  
           a. Virus diseases  
           b. Rickettsial diseases

---

Lieutenant General Robert Kho-sheng Lim, Chief of the Supervising and Planning Commission of the Chinese Army Medical Service, who has recently arrived in this country on a military mission, has given an interesting account of the methods used to meet China's critical shortage of trained medical personnel. This shortage is described by General Lim as "the Chinese Army's most serious medical problem." In Free China today, there are only about 6,000 fully trained physicians, he said. Only 3,000 of these are serving with the Chinese Army. To meet this shortage; eight thousand young Chinese men and women, many of them only 17 years of age and none over 25, are carrying the burden of medical treatment of wounded Chinese soldiers. These young people are known as junior medical aides, and go into the field after intensive training of six and even only three months.

The training of these medical aides is accomplished in six Emergency Service Training Schools which were organized partly with funds supplied by the American Bureau for Medical Aid to China and which are today being supported by funds obtained by United China Relief through the National War Fund. Only the most basic medical training and instruction in only the most common diseases can be given to the junior medical aides, since the need for their services is so great, Dr. Lim said. The training consists of instruction in first aid, in setting bones and treating fractures, in immunization, in preventive medicine and in general sanitation.

The efficacy of their training and the young people's efficiency in putting into practice their limited medical knowledge is shown partly by the fact that there has been no major epidemic in the Chinese Army or in China for six years.

The Emergency Medical Service Training Schools graduates go into small towns or villages near the front lines, and set up medical stations and dispensaries. "Civilians and soldiers alike are given medical treatment," said General Lim, "because in areas where the Chinese soldiers depend for food and other necessities upon the local population, and especially when they remain over long periods in one area, the good health of the civilians is essential. Many backward villages which never before had medical service of any kind, are now receiving it."

Shortage of equipment must often be handled with new methods, such as those used in vaccinations. In normal medical practice, an individual ampule of vaccine is used for each person. But because it is impossible to obtain materials for large quantities of ampules, the Chinese Army Medical Service is using large ampules containing sufficient vaccine for 100 vaccinations, and is administering to groups of 100 at a time.

General Lim organized the Chinese Red Cross Medical Relief Corps in 1937, and created hundreds of mobile operating units, known as "hospitals on muleback," which for seven years have operated as near as a half mile to the fighting lines. Last June, General Lim was awarded the Legion of Merit by President Roosevelt.

---

#### FUND FOR RESEARCH IN PSYCHOSOMATIC MEDICINE

The National Committee for Mental Hygiene announces the establishment of a fund for research in psychosomatic medicine to stimulate and subsidize research in the psychosomatic aspects of the diseases chiefly responsible for disability and death. The fund will be directed by Dr. Edward Weiss, Philadelphia, and administered under the direction of Dr. George S. Stevenson, New York, medical director of the National Committee for Mental Hygiene. Projects will be considered by a committee composed of Drs. Charles A. Aldrich, Rochester, Minn., Franz Alexander, Chicago, Stanley Cobb, Boston, John Romano, Cincinnati, and Lieut. Col. William C. Menninger. Additional information may be obtained from Dr. Weiss, 269 South 19th Street, Philadelphia 3.

---

The program for the Annual Meeting of the Association of Military Surgeons of the United States to be held at the Pennsylvania Hotel, New York City, November 2 to 4, incl., is being rapidly completed. In addition to addresses by the Surgeons General of the Army, Navy, and U. S. Public Health Service and by other distinguished guests, there will be formal papers, panel discussions and scientific and technical exhibits on the latest advances in military medicine.

---

#### DOCTOR DRAFT MAY ENDANGER U. S. HEALTH

Atlanta, Ga.—Dr. James E. Paullin, retiring president of the American Medical Association, in a nationwide CBS radio broadcast during the program, "The Doctor Fights" (June 6) warned against "an alarming situation" in medicine, seriously threatening the public health, because so many doctors are in the armed forces and it is difficult to obtain draft deferments for premedical students. Dr. Paullin asserted that "so hazardous is this situation as it relates to the health and welfare of the American people that several special committees of the American Medical Association are working seriously on this problem right now."

He pointed out that, in age groups over 45, "there are now more deaths among doctors than statistics would lead us to expect—simply because of the excessive strain placed upon these doctors by today's difficult times."

"Today with more than 60,000 doctors in the armed forces and with the Army and Navy taking more than half of the new graduates each year, an alarming situation has developed which in the future may seriously threaten the public health," he said.

"About 3,600 doctors are entering the armed services annually. There is an annual deficit each year of at least 2,200 doctors, because the vacancies created in medical ranks by death or forced retirement from practice because of age or illness cannot be filled. The reason for this lies in the difficulty of deferring premedical students, and in keeping our classes filled with otherwise draft-exempt men or with women.

"The problems of medical care are fundamental to the reconstruction and rehabilitation of our nation in the postwar period," he said. "The medical profession of this nation is willing to take the lead in planning the evolutionary changes that are bound to occur."

Medicine's most important current problem, Dr. Paullin asserted, "is the maintenance of a constant flow of physicians from our medical schools to supply the civilian population and the armed forces now and in the postwar period."

"The education of a modern doctor," he explained, "requires a period of premedical education. Even when it is accelerated to the utmost, it takes a year and a half. Then comes medical education which, even when speeded to the greatest rate, requires two and one-half years additional. Besides every doctor must have, even in wartime, at least nine months of internship in a good hospital. In peacetime this may be a year or even two years of additional training."

## OBITUARIES

## DR. VIRGIL EARL SIMPSON

Dr. Virgil Earl Simpson, F.A.C.P., an outstanding Internist of the South, died in Louisville, Kentucky, on May 3, 1944. Dr. Simpson was born on May 11, 1875, in Jefferson County, Kentucky. He obtained his A.B. in 1908 from the University of Louisville, and M.D. in 1900 from the University of Louisville School of Medicine. Part of his earlier career was spent as a high school teacher. He joined the faculty of the University of Louisville School of Medicine as instructor in pharmacology and therapeutics in 1902; subsequently he became Associate Professor and Clinical Professor of Medicine.

For many years he was member of the staff of the Louisville City Hospital, the Norton Memorial Infirmary, the Kentucky Baptist Hospital, St. Joseph's Infirmary, Masonic Widows & Orphans Home, and Kosair Hospital for Crippled Children. He was a member of the Revision Committee of the U. S. Pharmacopoeia; Captain of the Medical Corps, Kentucky National Guard, 1909-16; service on the Mexican border, 1916-17; Major in the Medical Corps, U. S. Army, 1918-19, with overseas service as Commanding Officer of Company Hospital No. 8, Montigny le Roi, France.

A Diplomate, with special certification in gastroenterology, of the American Board of Internal Medicine; formerly, Secretary, Treasurer, and President, Jefferson County Medical Society; Member of the Kentucky State Medical Association, Southern Medical Association, American Heart Association, American Gastroenterological Association. For several years he served in the House of Delegates of the American Medical Association. He became a Fellow of the American College of Physicians in 1921, and rarely missed a College meeting, contributed to the *ANNALS OF INTERNAL MEDICINE*, as well as the annual meetings of the College, and was the author of many published papers.

Dr. Simpson was a man of very strong convictions. He was strongly opposed to the Murray-Wagner-Dingell Bill, and his death came suddenly after completing a vigorous address to the First District Nurses Association of Kentucky against the provisions of this Bill. As a teacher, diagnostician and clinician he enjoyed an enviable reputation. It is doubtful if in the entire Southland, and certainly not in Kentucky, one has worked so unselfishly, tirelessly, and unceasingly, and contributed more to organized medicine, than has Dr. Simpson. He will be sorely missed by his many patients, the Medical Department of the University of Louisville, and the Medical Profession of the entire South.

C. W. DOWDEN, M.D., F.A.C.P.,  
Governor for Kentucky

## DR. HUGH FRANCIS CRAWFORD

Dr. Hugh Francis Crawford died at his home in Memphis February 18, 1944. In his death the South has lost a physician who stood for the highest principles in our profession. He was highly intelligent, industrious and studious. He kept himself well informed in medical progress and used his knowledge to great advantage in the treatment of his patients.

Dr. Crawford was born in Williston, Tennessee, on June 16, 1882. He attended the Vanderbilt University for his academic work and the Memphis Medical College for his medical training. He devoted a lot of time to post-graduate work, spending most of his time at Tulane University.

He practiced medicine for twenty years in Wilson, Arkansas, and twenty years in Memphis where he limited his work strictly to Internal Medicine. He was not only one of our leading physicians, but also built up a fine reputation as a teacher. He was an Associate Professor at the University of Tennessee Medical School.

He has been a Fellow of the American College of Physicians since 1936; a Diplomate, American Board of Internal Medicine; member, Southern Medical Association, Tennessee State Medical Association, Memphis and Shelby County Medical Society and West Tennessee Medical Society; Fellow, American Medical Association.

WM. CALVERT CHANEY, M.D., F.A.C.P.,  
Governor for Tennessee

## DR. MICHAEL ALBERT ALBL

Dr. Michael Albert Albl (Associate), Cleveland, Ohio, died February 19, 1944, of pneumonia at the age of 74. He was born October 8, 1869, and after completing a preliminary education was graduated from Western Reserve University School of Medicine in 1892. Dr. Albl also was a graduate pharmacist.

He was extremely interested not only in medicine, but in the field of literature, and was a member of the Cleveland Library Association and Cleveland Clinical Club. He was a member of the Academy of Medicine, Fellow of the American Medical Association, and was an Associate of the American College of Physicians since 1925. He was a member of the Staff of St. Alexis Hospital.

A. B. BROWER, M.D., F.A.C.P.,  
Governor for Ohio

## DR. WILLIAM EDWARD NESBIT

William Edward Nesbit, M.D., F.A.C.P., of San Antonio, Texas, died on April 5, 1944, after an illness of only three days, of virus pneumonia. He was in his fifty-sixth year.

Dr. Nesbit graduated from Johns Hopkins University Medical School in 1913, and after serving as interne in hospitals in Roanoke, Virginia, and Baltimore, Maryland, he entered the Regular Army Medical Corps in 1917. Graduating from the Army Medical School, he went overseas with the Ninetieth Division in 1918, and was seriously wounded at St. Mihiel. At the end of the War, after his recovery, he settled in San Antonio, Texas, limiting his work exclusively to Internal Medicine. He was for many years Chief of Medical Service of the Robert B. Green Memorial Hospital. Besides being a member of the State, Southern, American Medical, and American Heart Associations, he was one of the organizers of the Texas Club of Internists, and since 1928 a Fellow of the American College of Physicians.

At the time of his death Dr. Nesbit was Chairman of the local Committee on Procurement and Assignment, Chairman of the Screening Committee of the Selective Service for more than two years, and devoted one-half of each day examining at the Induction Center, Dodd Field. A colleague has stated that "Dr. Nesbit was one of the honest and therefore one of the kindest and gentlest of men. Medicine to him was never a business and it was always more than a science. He cared for neither wealth nor fame, but loved his work because it furnished him with an opportunity to comfort and to help all those who suffer pain."

He is survived by his widow, Mrs. Fairfax Janin Nesbit, a daughter Fairfax Janin, and a sister Mrs. Zoie Nesbit Strother.

M. D. LEVY, M.D., F.A.C.P.,  
Governor for Texas

#### DR. ROLAND N. KLEMMER

The sudden and untimely death of Dr. Roland N. Klemmer on May 9, 1944, has come as a shock to all who knew him. Dr. Klemmer had been on active duty with the Medical Corps of the United States Navy, as a Lieutenant Commander, since December 29, 1941, when he volunteered for service. At the time of his death, he was stationed in New Caledonia, where he had been in charge of the medical section of a naval mobile hospital.

Dr. Klemmer was born in Springfield, Massachusetts, in 1898. He received his A.B. degree in 1918 from Franklin and Marshall College, and was graduated in 1922 from the University of Pennsylvania School of Medicine. Dr. Klemmer later availed himself of postgraduate study in cardiology at the University of Pennsylvania Graduate School of Medicine and Harvard Medical School.

Shortly after receiving his medical degree, he became Pathologist at the Lancaster General Hospital, where he served for some years. Following this, he became Cardiologist and Chief of Staff at the Lancaster General Hospital, and from 1933 to 1938, Dr. Klemmer was Chief of Staff at the Lancaster County Hospital. Prior to going on active duty with the Navy, he resided in Lancaster, Pennsylvania.



Dr. Klemmer was a member of the Lancaster County Medical Society, Pennsylvania State Medical Association and American Medical Association. He was a Fellow of The American College of Physicians since 1930, and was likewise a Diplomat of the National Board of Medical Examiners and American Board of Internal Medicine.

In addition to the personal loss to his fellow associates and friends, medicine has lost one of its most capable students and staunch supporters. Dr. Klemmer was an inspiring leader in the medical profession, and his passing is acknowledged with humble tribute.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

### DR. JACOB EARL MEENGs

Dr. Jacob Earl Meengs, F.A.C.P., died February 2, 1944, of valvular heart disease, arteriosclerosis and general edema with pleuritic effusion on the right side.

Dr. Meengs was born in Holland, Michigan, August 4, 1881, and received his M.D. at Rush Medical College in 1904. He was Resident Physician in Lennox Hill Hospital, New York City, from 1911 to 1913, and did postgraduate work in 1913 and 1914 at the Victoria Augusta Hospital, Berlin, Germany, and at the Allgemeine Krankenhaus, Vienna, Austria. He was a member of Kent County Medical Society and Michigan State Medical Society; Fellow of the American Medical Association and of the American College of Physicians; Diplomat, American Board of Internal Medicine.

Dr. Meengs was not known to the writer, but I am advised by those of his colleagues who knew him best that he was a quiet, reserved, studious man, slow to take up new methods, but respected by his fellow practitioners and the public.

P. L. LEDWIDGE, M.D., F.A.C.P.,  
Acting Governor for Michigan

### DR. FRANK BOLLES WAKEMAN

Colonel Frank Bolles Wakeman, who was a Fellow of the American College of Physicians, died March 17, 1944, at Fort Monmouth, New Jersey, of a coronary occlusion.

Colonel Wakeman was born at Sidney, New York, on May 15, 1896. He graduated in pharmacy from Valparaiso University in 1915, received his degree in pharmaceutical chemistry in 1916 and a B.S. in chemistry from the same school in 1917. From August 1917 to May 31, 1919, he served as first lieutenant, infantry, Officers Reserve Corps, going overseas with the 369th U. S. Infantry. After several years spent in the educational field, part of the time as a high school principal, he matriculated at the Indiana University School of Medicine, where he received his M.D. in 1926. After

graduation and the completion of an internship at Walter Reed General Hospital, he practiced medicine in Indiana until 1928 when he was appointed a first lieutenant in the Medical Corps, Regular Army. He was promoted to captain, U. S. A., on June 3, 1928, major, U.S.A., on June 4, 1937, lieutenant colonel, A.U.S., on February 1, 1942, and colonel, A.U.S., on September 8, 1942.

During his Army career Colonel Wakeman continued his scientific studies, receiving the degree of Master of Arts from Catholic University of America in 1933 and the degree of Doctor of Philosophy from the same institution in 1935. In 1937 he earned the degree of Doctor of Public Health from Johns Hopkins School of Public Health. Service courses which he completed were the basic course, Army Medical School, in 1929, and the advanced course, Army Medical School, in 1936; the basic course, Medical Field Service School, Carlisle Barracks, in 1929, and the advanced course at the same school in 1938; and the Command and General Staff School, Fort Leavenworth, Kansas, in 1940. Teaching assignments during this period included a tour as instructor in biochemistry at the Army Medical School from 1932-1936, and a tour as instructor in sanitation at the Medical Field Service School from 1937-1939. In 1938 he was awarded the Henry Wellcome prize by the Association of Military Surgeons of the United States for his essay on "A Specific Somatic Polysaccharide as the Essential Immunizing Antigen of the Typhoid Bacillus."

In February 1940 Colonel Wakeman was assigned to the Training Division, Surgeon General's Office, and became its director in July of the same year. While serving in that capacity Colonel Wakeman laid the plans and was more responsible than any other man for the execution of the vast training program of the Medical Department during the current emergency and war. It is indeed fortunate that a man of such foresight, organizing ability, and energy was available to the Medical Department during this period.

NORMAN T. KIRK, Major General, U.S.A.,  
A.C.P. Governor

#### DR. JACOB GUTMAN

Dr. Jacob Gutman, F.A.C.P., Brooklyn, New York, died in the Presbyterian Hospital, May 7, 1944, following a short illness. He was born in Riga, Latvia, June 22, 1876; attended the Alexandre Gymnasium and the School of Catherine the Great, Riga; M.D., 1900, Cornell University Medical School; Phar.D., 1914, University State of New Jersey; for many years, Medical Director of the Brooklyn Diagnostic Institute; Consulting Physician, Manhattan General (New York City), Shore Road, Boro Park General, Riverdale and Williamsburgh Maternity Hospitals; Chief Medical Diagnostician and Honorary Surgeon, New York City Police Department.

Dr. Gutman was a member of his county and state medical societies, American Medical Association, American Therapeutic Society, American Congress of Physical Therapy, American Medical Editors and Authors Association, Williamsburgh Medical Society, East New York Medical Society and others. . He had been a Fellow of the American College of Physicians since 1920. He was the author of many published papers, and of "Modern Drug Encyclopedia and Therapeutic Guide."

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

### DR. HARRY J. BELL

Dr. Harry J. Bell, F.A.C.P., Dawson, Pa., died September 30, 1943, aged 76. Dr. Bell was born at Arendtsville, Adams County, Pa., in 1868. He attended the public schools and spent one year in the preparatory department at Muhlenberg College. He received his Medical Degree from the Medico-Chirurgical College of Philadelphia in 1892. For many years, he had been on the staff of the Connellsville State Hospital. He was a member of the Fayette County Medical Society, Pennsylvania State Medical Society, American Medical Association, and had been a Fellow of the American College of Physicians since 1924.

# ANNALS OF INTERNAL MEDICINE

VOLUME 21

AUGUST, 1944

NUMBER 2

## GLYCOSURIA IN MENINGITIS \*

By FRANK FERGUSON, M.D., and DAVID BARR, M.D., F.A.C.P.,  
*New York, N. Y.*

SINCE 1884<sup>1</sup> there have been in the literature scattered references to the occurrence of glycosuria in meningitis. Some have been in the form of case reports, and in several emphasis has been placed on the rarity of the association. Our interest in the subject was excited by the admission to the New York Hospital of a comatose woman of 41 with signs both of meningitis and of diabetic coma. Therapy begun simultaneously for both conditions

TABLE I

Etiology	Total Cases	No Glycosuria	Initial Glycosuria with Previous History of Glycosuria	Post-Infusion Glycosuria	Unexplained Initial Glycosuria
Meningococcus	26	14	1	2	9
Pneumococcus	8	3	1	3	1
Staphylococcus	8	4		2	2
Lymphocytic chorio meningitis	3	2		1	
Streptococcus	2	1		1	
<i>E. coli</i>	1	1			
<i>H. influenzae</i>	2	2			
Tubercle bacillus	6	4		1	1
Syphilis	3	2		1	
Mumps	2	2			
Toxoplasma	1	1			
Unknown	10	6		3	1
Total	72	42	2	14	14

resulted in uneventful recovery from the meningitis and in the prompt disappearance of glycosuria. A study of this case led to a review of the records of patients admitted to the New York Hospital during the preceding four years, with the specific purpose of determining the incidence of glyco-

\* Received for publication April 15, 1944.

From the Department of Medicine, New York Hospital and Cornell University Medical College, New York City.

suria or other evidences of disturbed carbohydrate metabolism in the course of meningitis.

Records were found of 72 cases of meningitis, 30 of whom showed glycosuria. Fourteen of the 30 cases had received infusions of dextrose solution at some time before the appearance of glycosuria. In the remaining 16 cases, cause for the glycosuria other than the meningitis itself was not immediately evident. In table 1 the cases of meningitis are listed according to their etiology. Table 2 displays certain details of the 16 cases which had unexplained glycosuria. Further details of these cases are presented in the following summaries.

TABLE II

Case No.	Sex	Age	Causative Organism	Glycosuria		Acetonuria		Initial Blood Sugar	Initial C.S.F. Sugar	Initial CO <sub>2</sub>	Insulin Units	Previous Evidence Diabetes
				Maximum	Duration Days	Maximum	Duration Days					
1	F	8	Meningococcus	++	2	+	3	155	103	29	0	No
2	F	36	Meningococcus	++	2	++	1	153	10	54	0	No
3	M	34	Meningococcus	++	2	++	2	244	3		0	No.
4	M	6	Meningococcus	++++	3	++	1		5		0	No
5	F	18	Meningococcus	++	1	++++	2		0		75	No
6	M	16	Meningococcus	+++	1	0		122	0		0	No
7	F	19	Meningococcus	++	1	0		150	26		0	No
8	M	47	Meningococcus	++++	10	++	1	209	110	69	20	No
9	F	26	Meningococcus	++++	3	+++	3	212	10		0	No
10	F	18	Meningococcus—?	+++	3	++	3		59		0	No
11	M	4	Pneumococcus	++++	3	++	3		51	48	0	No
12	F	13	Staphylococcus	+	2				59		0	No
13	M	49	Staphylococcus	++	1						0	No
14	M	43	Tubercle	+	1				0		0	No
15	F	57	Pneumococcus	++	6	++++	1		140		900	Yes
16	F	41	Meningococcus	++++	2	++	1	441		14	245	Yes

*Case 1.* A girl of 8 one year before entering the hospital had a urine examination which was negative for sugar. She was admitted after a few hours of fever, headache, vomiting, delirium, and semi-coma. Examination revealed numerous petechial spots, a stiff neck, strabismus, drowsiness, hyperactive reflexes, and bilateral positive Babinski reflexes. At the time of admission her blood sugar was 155 mg. per cent, CO<sub>2</sub> capacity 29 vol. per cent, white blood cells 21,300. Cerebrospinal fluid was cloudy with 11,000 white blood cells, Pandy 3+, sugar 103 mg. per cent. Meningococci were cultured from both blood and spinal fluid. She was treated with sulfadiazine for 13 days. On the second day her urine showed a trace of sugar and a faint trace both of acetone and of diacetic acid. The CO<sub>2</sub> capacity had risen to 53 vol. per cent. On the third day there was still a faint trace of acetone but thereafter the urine was normal. The temperature became normal on the fourth day, the leukocyte count on the fifth day. Blood sugar was 96 mg. per cent, the blood culture was negative and the cerebrospinal fluid had become almost normal on the seventh day. Convalescence was uneventful and she was discharged without symptoms on the fifteenth day. Two months later she was reported to be entirely well.

*Case 2* was a woman of 36, whose urine examination two years before had been entirely negative. She was admitted to the hospital following a week of upper res-

piratory infection, two days of muscle aching, chills and restlessness, and a few hours of headaches, vomiting and stiff neck. On examination she was semi-comatose with a temperature of 40° C., signs of meningeal involvement and a hemorrhagic rash. Examination of her urine showed sugar 2 +, acetone 2 +, diacetic acid 4 +, leukocytes 9,900, fasting blood sugar 153 mg. per cent, CO<sub>2</sub> capacity 54 volumes per cent. The cerebrospinal fluid contained 36,000 white blood cells and had a sugar content of 10 mg. per cent. Meningococci were cultured from the spinal fluid. She was treated with sulfadiazine, intravenous glucose, and sodium bicarbonate. The meningeal signs cleared in a few days. On the second day, urine sugar was 2 +, acetone 0, diacetic acid 2 +. The urine was negative thereafter. She appeared to be completely well at the time of discharge from the hospital. Seven months later she was in robust health without residuals and with no signs of diabetes. Glucose tolerance tests\* were as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.
5th day	86	176	208	160	
6th day	81	185	175	202	116
Urine sugar	0	0	0	0	0
7 mos. later	85	158	125	83	78
Urine sugar	0	0	0	0	0

*Case 3* was a man of 34 who two weeks before entry to the hospital had a mild upper respiratory infection. One week previously he had developed muscle aches, a transient pin-point rash, and chilly sensations. For two days he had been drowsy and had suffered from anorexia. Vomiting started one day before admission with headaches and increasing stupor. Examination revealed a temperature of 38.3° C., stupor, dehydration, slight strabismus, and signs of meningeal involvement. Urine examination revealed sugar 2 +, acetone 2 +, diacetic acid 4 +. Blood sugar was 244 mg. per cent. The leukocyte count was 26,000. The cerebrospinal fluid contained 25,000 leukocytes and 3 mg. per cent of sugar. Gram negative diplococci were seen on smear. He was treated with sulfadiazine and sodium bicarbonate. On the second day the urine sugar was 1 +, acetone 1 +, diacetic acid 1 +. Thereafter the urine was normal. On the second day the cerebrospinal fluid sugar had a value of 74 mg. per cent. On the fourth day he was asymptomatic. His convalescence was entirely uneventful. Sugar tolerance tests were as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.	4 hr.
13th day	84	142	122	108	76	85
Urine sugar	0	0	++++	0	++++	0
8 mos. later	88	155	131	92	103	
Urine sugar	0	0	±	0	0	

*Case 4* was a boy of 6, whose urine had been negative for one year before admission. He came into the hospital after two days of fever, malaise, vomiting, neck pain and delirium. Examination showed a temperature of 38.2° C., dehydration, opisthotonos, petechial spots and moderate signs of meningeal involvement, urine sugar 4 +, acetone 2 +, diacetic acid 2 +. He was treated with sulfadiazine and intravenous glucose and with paraldehyde as a sedative. On the third day his urine showed a trace of sugar but was normal thereafter. Meningococci were cultured from the cerebrospinal fluid which had a sugar content of 5 mg. per cent. He recovered

\* Unless otherwise specified sugar tolerance tests were performed after the administration of 100 grams of glucose by mouth.

and was discharged on the eighteenth day. His condition appeared to be entirely normal on the follow-up examination which, however, included no special studies of his carbohydrate metabolism.

*Case 5.* A girl of 18 had had an upper respiratory infection for 11 days and fever, headache, vomiting, and rather severe muscle pain for 24 hours. Her examination revealed a temperature of 42.5° C., dehydration, restlessness, semi-coma, injected pharynx, and signs of meningeal involvement. Urine examination showed sugar 2 +, acetone 4 +, diacetic acid 1 +, leukocyte count was 33,100; blood cultures were negative. Meningococci were cultured from the spinal fluid which contained 23,100 leukocytes but no sugar. She was treated with infusions and with doses of regular insulin amounting to 75 units in the first five hours. Her urine was clear after six hours except for a trace of acetone on the second day. She received sulfadiazine or sulfamethazine for a period of 10 days. After the seventh day she was asymptomatic except for bilateral seventh and ninth nerve palsies which had started on the second day. Sugar tolerance on the twelfth day was:

	Fasting	1 hr.	2 hr.	3 hr.
Blood sugar	90	127	136	114
Urine sugar	0	+	0	0

She was discharged on the fifteenth day and one and a half months later had no signs of paralysis. Four months later she appeared to be entirely well except for sinusitis.

*Case 6* was a boy of 16, who one day preceding his admission to the hospital became irrational with fever, headache, chills and vomiting. Examination revealed temperature of 42.4° C., conjunctivitis, signs of meningeal involvement and semicoma. Examination showed urine sugar 3 +, acetone 0, diacetic acid 1 +, leukocyte count 25,200, blood sugar 122 mg. per cent, blood culture negative. Meningococci were cultured from the cerebrospinal fluid which contained 15,000 leukocytes. The sugar content of the fluid was too low to read. He was treated with sulfadiazine for eight days. The urine became negative on the second day and he was asymptomatic after the seventh day. He was discharged from the hospital as cured on the sixteenth day. Nine months later there were no residuals of meningitis and no signs or symptoms of diabetes. Sugar tolerance tests were as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.
2 mos. later	89	96	85	70	101
9 mos. later	98	130	70	70	69

*Case 7.* A girl of 19 ten days before entry had had chills, fever, malaise, and a petechial rash. The eruption disappeared after about two days. Three days before entry she suffered from shaking chills, fever and headache. For one day she had had vomiting, stiff neck, drowsiness, increasing headache and a skin rash. Examination revealed a temperature of 37° C., blood pressure 110 mm. of Hg systolic and 70 mm. diastolic, an erythematous eruption and signs of meningeal involvement, urine sugar 2 +, acetone 0, diacetic acid 0, leukocyte count 20,000, blood sugar 150 mg. per cent, negative blood cultures. Meningococci were cultured from the cerebrospinal fluid which contained 23,000 leukocytes and 26 mg. per cent of sugar. She was started on sulfadiazine but because of hematuria was shifted after 24 hours to sulfamethazine which was continued for a period of 10 days. The urine was negative on the second day and remained so thereafter. She herself was asymptomatic after the fourth day.

Her convalescence was uneventful, and she appeared to be entirely well one month after her discharge from the hospital. Sugar tolerance tests were as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.
5th day	77	212	268	211	74
Urine sugar	0	0	++	+++	+++
13th day	85	127	150	117	145
Urine sugar	0	+	+++	++	0

*Case 8* was a man of 47, who for two weeks had had an upper respiratory infection. For 24 hours he had had headache, profound weakness, and increasing stupor. At the time of admission he was semicomatose and had a petechial eruption. His thyroid was diffusely enlarged and the liver could be felt five fingers' breadth below the costal margin. There were definite signs of meningeal involvement. His blood pressure was 185 mm. of Hg systolic and 105 mm. diastolic and the temperature was 38.3° C. Urine examination revealed sugar 4+, acetone 2+, diacetic acid 4+. Blood sugar was 209 mg. per cent. Meningococci were cultured from the cerebrospinal fluid which contained 9,900 leukocytes and which showed 4+ Wassermann reaction. He was treated with sulfadiazine for 11 days. The meningeal signs had disappeared by the tenth day. The cell count and Wassermann reaction in the spinal fluid were normal on the seventeenth day. Acetone had disappeared from the urine on the second day but glycosuria continued from 2+ to 4+ for eight days, was negative on the ninth day, 2+ on the tenth and negative thereafter. During this period it was suspected that he might be diabetic. Insulin was given tentatively in doses of 10 units on the sixth and seventh days of his illness but was discontinued thereafter. On the seventeenth day liver function tests revealed no abnormalities and his basal metabolic rate was plus 2. At the time of his discharge from the hospital he had entirely recovered from the meningitis. His thyroid gland and his liver were enlarged as at the time of admission. Two weeks later his urine was found to contain 3+ sugar. Five months after discharge no sugar or acetone was demonstrable. Three months after leaving the hospital he was employed as a dishwasher and was able to continue this work without special treatment and with no recognizable signs or symptoms of diabetes. The sugar tolerance tests were as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.	4 hr.
4th day	182	212	280	313	330	322
Urine sugar	0	0	++		++++	
12th day	124	241	270	320	224	133
Urine sugar	0	0	++	+++	+++	0
29th day	119	202	280	295	189	

*Case 9* was a woman of 26 who for two days had suffered from muscle pains, headache, and fever and for 24 hours, from vomiting. Examination showed disorientation with temperature of 38.9° C., hemorrhagic rash and signs of meningeal involvement. Urine showed sugar 3+, acetone 3+, diacetic acid 0. Blood contained 31,000 leukocytes and 212 mg. per cent of sugar. Blood cultures were negative. Meningococci were grown from the cerebrospinal fluid which contained 31,000 leukocytes and 10 mg. per cent of sugar. The Wassermann reaction was 4+ in the first spinal fluid but gradually became less positive and finally negative in subsequent examinations. She was treated with sulfadiazine for 12 days. On the second day the urine showed sugar 4+, acetone 3+; on the third day, sugar 2+, acetone 2+



but neither sugar nor acetone thereafter. Weakness of the left lateral rectus muscle started on the third day but gradually disappeared. She was discharged on the sixteenth day without symptoms except for a diplopia which persisted for two months. Six months later she showed no signs of diabetes, no weakness of the extraocular muscles. There was, however, a fine tremor of the hand; her pulse rate was 92 under resting conditions; she had rapid changes in mood and was easily irritated. Her appetite was very vigorous and she gained 16 pounds during the six months following her discharge. Graves' disease was suspected and she was given iodine therapeutically for a period of 4 months, without change in her state. At no time did she develop the eye signs of hyperthyroidism; the thyroid gland was never enlarged. Sugar tolerance tests were as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.
11th day	90	207	208	134	122
Urine sugar	0	+	+++	++	0
14th day	98	173	190	131	100
Urine sugar	0	0	0	0	0
6 mos. later	104	182	161	114	61
Urine sugar	0	+	++	0	0

*Case 10.* A girl of 18 had suffered for two days from fever, chilly sensations, and cough. Examination showed a temperature of  $39.2^{\circ}$  C., blood pressure of 108 mm. of Hg systolic, 64 mm. diastolic, signs of a pneumonia at the right lower lobe and no meningeal signs. Urine sugar was 3+, acetone 2+, diacetic acid 1+. The leukocyte count was 7,100 and cultures of the blood were negative. The cerebrospinal fluid was clear, contained 1 cell and 80 mg. per cent of sugar. She was treated with sulfadiazine and infusions and was given paraldehyde as a sedative. Twelve hours after admission her neck became stiff and she developed positive Kernig and Brudzinsky signs. Her spinal fluid contained 19,000 leukocytes with a 4+ Pandy and a sugar content of 59 mg. per cent. On the second day her urine showed sugar 3+, acetone 2+, diacetic acid 0; on the third day, 3+ sugar, 2+ acetone. Thereafter it was negative. The meningeal signs cleared in a few days and the pneumonia resolved on the eleventh day. She was discharged without symptoms. Two and a half months later she felt well and had no signs of diabetes. Her sugar tolerance at that time was as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.
$2\frac{1}{2}$ mos. later	104	178	100	94	94
Urine sugar	$\pm$	0	$\pm$	$\pm$	0

Possibly because of early sulfonamide treatment all cultures were negative both in blood and spinal fluid. Although the etiological agent was not determined the case was considered, because of its clinical picture, one of meningococcemia with later development of meningococcic meningitis.

*Case 11* was a boy of 4, who for four days had had headaches with fever, loss of appetite and vomiting and for one day dyspnea, projectile vomiting and convulsions. At the time of admission paraldehyde and ether anesthesia were required for control of violent spasms. He had signs of meningeal involvement and a right flaccid paralysis of the face and body. Urine sugar was 4+, acetone 2+, diacetic acid 0. Pneumococcus Type XVIII was cultured from the spinal fluid which contained 2,600 leukocytes and 51 mg. per cent of sugar. Blood cultures were negative.

He was treated with sulfadiazine, infusions, and type XVIII horse serum. The urine showed sugar 2 +, acetone 1 +, on the third day but was normal thereafter. On the ninth day the skull plate showed signs of increased intracranial pressure and mastoiditis. On the twelfth day he was asymptomatic except for right hemiparesis and aphasia. Sulfadiazine was discontinued on the sixteenth day. On the twentieth day he spoke a little and the paralyzes were less marked. He was discharged on the forty-ninth day with only partial paralysis of the right arm. One and a half years after his acute illness he had attacks suggestive of petit mal and had developed spastic paralysis with contractures in the right arm. He was otherwise well. No urines were obtained but no signs or symptoms of diabetes were noted.

*Case 12.* A girl of 13, with staphylococcic meningitis, had a faint trace of sugar in the urine during the first two days of her illness. There was no previous history of diabetes or of glycosuria and no other data concerning carbohydrate relationships were obtained. She died on the third day of observation.

*Case 13.* A man of 49, with staphylococcic meningitis, brain abscess and empyema had a trace of sugar in his urine during the first day in the hospital. No other observations on carbohydrate metabolism were made before his death on the fifth day.

*Case 14.* A man of 43, with tuberculous meningitis, had a faint trace of sugar in his urine on the first day following his entry to the hospital. Two months previously his blood sugar level had been found to be 71 mg. per cent. No observations were made on his blood sugar or other carbohydrate relationships during the four days intervening between his entry and his death.

*Case 15* was a woman of 57 who six weeks before admission had had a nasal catarrh, gradual loss of hearing, tinnitus, and pain in the left ear. The local doctor found only slight injection of the drum and no mastoid pain. Four weeks before she was admitted to the hospital her physician discovered glycosuria with a blood sugar of 186 mg. per cent. He treated her with 10 units of protamine insulin each day and with a diet containing 70 grams of protein, 100 gm. of fat, and 200 gm. of carbohydrate. During a period of six months she had lost about 30 pounds. For two weeks before her entry to the hospital she had suffered from increased thirst and slight pruritus vulvae and for one day with chill, fever, increasing pain in the left ear and a stiff neck. Examination revealed a temperature of 40.6° C., dehydration, stiff neck, left purulent otitis media, acetone breath, drowsiness, and signs of meningeal involvement. The urine sugar was 2 +, acetone 4 +, diacetic acid 3 +. Blood culture was negative and leukocytes were 14,800. *Pneumococcus* Type III was cultured from the spinal fluid, which had a 1 + Pandy and contained 3,500 leukocytes and 140 mg. per cent of sugar. She was treated with sulfadiazine, with intravenous glucose, and insulin. During the first 11 days the dosage of insulin varied from 35 units to 95 units. It was then reduced to 15 units and so continued for 13 days. Myringotomy yielded only one small drop of pus. A simple mastoidectomy performed on the second day showed extensive mastoid necrosis with dural involvement. At that time her urine still showed 4 + sugar but no acetone. On the third day cultures of the cerebrospinal fluid were negative, the patient felt much improved with a glycosuria of 2 +. She was asymptomatic on the sixth day with urine sugar 2 +, blood sugar 103 mg. per cent. Thereafter only slight traces of sugar were found. On the ninth day an attack of dizziness was attributed to a hypoglycemic reaction although the blood sugar on that morning had been 242 mg. per cent. On the eleventh day the blood sugar was 202 and on the sixteenth day 190 mg. per cent. On the twenty-fourth day she was depressed and agitated and it was thought that the insulin dosage might be contributing to her mental state. Insulin was discontinued and thereafter she remained completely well with no glycosuria and with no further need of insulin. On the twenty-seventh day her blood sugar was 146 mg. per cent, and on the thirty-seventh day sulfadiazine was discontinued. She was discharged without

symptoms on the forty-sixth day. Ten months later she had taken no insulin, had gained 19 pounds, and had eaten an unrestricted diet without excessive appetite, polydipsia, polyuria or pruritus vulvae. She felt entirely well except for slight left mastoid pain and a continuous tinnitus of a totally deaf left ear. Repeated urine examinations by her home physician showed no sugar. Her sugar tolerance at this time, however, was as follows:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.
	184	259	360	396	315
Urine sugar			+++	++++	++++

*Case 16* was a woman of 41 who had had three previous admissions to the hospital. The first, 18 months previously, had been for the treatment of pernicious anemia and bronchiectasis. During her stay in the hospital she showed on several occasions traces of sugar in her urine. The second admission nine months previously was because of a pneumococcus Type III infection of the mastoid. During the first 10 days of this period her urine contained sugar in amounts varying from 1 + to 4 +. Her admission sugar, however, was only 96 mg. per cent and a glucose tolerance on the eleventh day was within normal limits:

Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.
90		140	150	69

Her third admission was for plastic closure of the mastoid, and at this time she showed no glycosuria. Her fourth admission had been preceded by one day of fever, chills, joint pains, vomiting, rash, headache, and stiff neck. Examination revealed a temperature of 39.4° C., blood pressure of 88 mm. Hg systolic and 58 mm. diastolic, slight cyanosis, opisthotonos, hemorrhagic skin eruption, and signs of meningeal involvement. She was in deep coma and had a strong acetone breath. Urine sugar was 4 +, acetone 2 +, diacetic acid 4 +, blood sugar 441 mg. per cent, CO<sub>2</sub> combining power 14 vol. per cent, calcium 10 mg. per cent. Blood cultures were positive for meningococcus, which was also found on smear of the cerebrospinal fluid. The leukocyte count in the fluid was 1,800. She was treated with sulfadiazine, intravenous glucose, M/6 molar sodium lactate and 245 units of insulin in 12 hours. At the end of the first day her urine was negative, her blood sugar was 33, the CO<sub>2</sub> combining power 66. Insulin was discontinued. On the second day the urine sugar was 2 +. Thereafter the urine was normal. She was asymptomatic on the seventh day and was discharged as cured. Thirteen months later it was found that her anemia was poorly controlled and that her teeth were troubling her. She had no signs or symptoms of diabetes. On the twentieth day and again 13 months later intravenous sugar tolerance test with 50 c.c. of 50 per cent glucose revealed the following:

	Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.	4 hr.
20th day	73	192	114	77	53	78
Urine sugar	0	++++	0	0	0	0
13 mos. later	118	175	86	63	76	
Urine sugar	0	+++	+	0	0	

She was seen in the outpatient department 16 months after discharge from the hospital without symptoms of diabetes and without glycosuria.

## COMMENT

Of the 16 cases exhibiting glycosuria without obvious explanation, three died during the acute stage of the disease and observations were too limited to permit opinion whether the glycosuria was a concomitant of the meningitis or an evidence of some more long standing disturbance in the carbohydrate metabolism. Twelve of the 16 (1-11, 16) appeared at some interval after the subsidence of acute symptoms to be entirely free from any clinical evidence of diabetes. In six of the 12 (2, 3, 6, 9, 10, 16) this impression was confirmed by sugar tolerance curves which could be considered within normal limits. In three of the 12 cases no sugar tolerance curves were obtained after the subsidence of the acute illness. In three cases there was a question of a previous or accompanying diabetic or prediabetic state. Those cases require some further comment and analysis.

In case 8 the glycosuria persisted for 10 days and then ceased. Sugar tolerance curves taken on the fourth, twelfth, and twenty-ninth days, however, were abnormal. Furthermore glycosuria was demonstrated two weeks after the patient's discharge from the hospital. Five months later there was no sugar or acetone in the urine and the patient was working regularly without symptoms and without recourse to insulin. Unfortunately no sugar tolerance curves could be obtained at that time. In spite of these later observations indicating freedom from clinical diabetes, the possibility of a more or less permanent defect in the carbohydrate metabolism could not be excluded, and it was thought that the patient might have been suffering from a prediabetic condition which was exacerbated by the acute illness. That the abnormal sugar tolerance curves and the recurrent glycosuria were not due to the enlarged thyroid is indicated by a normal basal metabolic rate. The possibility that the enlargement of the liver was due to hemochromatosis was considered but could not be proved.

Case 15 presented a most interesting problem. She had exhibited glycosuria and had been treated for diabetes before the onset of her meningitis. This difficulty had begun two weeks after an otitis media and preceded by four weeks the onset of the meningitis. The diabetic state appeared to be exaggerated by the meningitis, and for a time doses of 35 to 95 units of regular insulin were required for its control. Following *mastoidectomy*, however, her condition rapidly improved. The glycosuria disappeared and it did not recur when insulin was discontinued. Ten months later she was symptom-free on an unrestricted diet without insulin. At that time, however, her fasting blood sugar was still 186 mg. per cent and the curve of blood sugar following the ingestion of glucose revealed a diminished tolerance. It seemed necessary to conclude that this patient was a mild diabetic in whom otitis media, mastoiditis and meningitis produced a temporary exacerbation.

It was case 16 that originally attracted our attention to the question of glycosuria in meningitis. During two of her previous admissions—one for

pernicious anemia and bronchiectasis, and the other for a pneumococcal infection of the mastoid—sugar had been found in her urine. This might have been regarded as evidence of diabetes if a sugar tolerance test during one of these admissions had not been within normal limits and if in the intervals she had not been quite free from symptoms suggesting the disease. The clinical picture at the onset of meningitis mimicked diabetic coma with 4 + sugar, 4 + diacetic acid, blood sugar 441 mg. per cent, and CO<sub>2</sub> capacity 14 vol. per cent. Dosage of 245 units of insulin during the first 12 hours was thought to be necessary. By the second day, however, insulin was discontinued, and the urine remained normal thereafter. Sugar tolerance curves were normal on the twentieth day and again 13 months later. Doubt must be entertained concerning the diagnosis of diabetes in this patient although the frequent glycosuria is evidence of an easily induced disturbance of carbohydrate metabolism.

Case 10 deserves comment for a different reason. At the time of admission, she was suffering from a generalized infection thought but not proved to be meningococcal septicemia. Glycosuria was present at this time. It was not until 12 hours later that signs of meningitis developed. Glycosuria was not notably increased after the meningitis became evident.

### DISCUSSION

This study reveals that glycosuria is by no means an infrequent accompaniment of the onset of meningitis. Of 32 cases, 16 showed sugar in the urine. Of these three may have been diabetic or pre-diabetic. In the remainder the glycosuria was unexplained. The phenomenon was encountered in meningitis due to meningococcus, pneumococcus, staphylococcus, and the tubercle bacillus. It was also found in one case of acute meningitis in which the etiology was not established. The meningococcic cases constituted by far the greatest number of the series, and of the 26 examples of meningococcic infection more than one third (34.6 per cent) showed unexplained glycosuria.

Of the 13 glycosuric cases in which tests for acetone and diacetic acid were made ketosis was demonstrated in 11. There was no constant relationship between glycosuria and the presence of ketone bodies in the urine. In two cases of glycosuria acetone was not demonstrated and in several with 4 + sugar reactions the ketosis was mild. Furthermore among the 44 cases which showed no glycosuria, 10 exhibited ketone bodies in appreciable amounts.

Usually the glycosuria was transient. It disappeared in all the cases and persisted beyond the third day in only three of the 16.

The literature concerning glycosuria in meningitis consists for the most part of reports of scattered cases and of experiences with small groups. It embraces examples of meningitis of the most diverse etiology. One of the earliest articles was that of Frew and Garrod,<sup>2</sup> who reported 41 cases of

tuberculous meningitis, in 15 of which marked glycosuria was demonstrated. In 11 others the urine partially reduced Fehling's solution. They found glycosuria a late manifestation, and in most of their cases sugar appeared within the last 48 hours of life. Nohecourt<sup>3</sup> reported a case of tuberculous meningitis in which vomiting and acetoneuria were followed by the appearance of moderate amounts of sugar in the urine. Another case of tuberculosis of the meninges studied by Krafchik and Slobody<sup>4</sup> exhibited glycosuria at the onset of the infection. Stupor with urinary sugar 4 +, acetone 3 +, blood sugar 200 mg. and CO<sub>2</sub> combining power 36 vol. per cent led to the diagnosis of diabetic coma. Treatment with insulin which corrected the glycosuria and ketonuria and caused a hypoglycemic reaction did not control the stupor, thus permitting recognition of the meningitis.

Glycosuria without ketosis in a 40 year old man with pneumococcus Type II meningitis was reported by Roussel.<sup>5</sup> Although the later condition of the patient is not described, it is inferred that there was no suspicion of permanent diabetes.

Taylor and McKinstry<sup>6</sup> reported a case of suppurative meningitis which developed in the course of pneumonia and which exhibited at onset coma and glycosuria without ketosis. The urine sugar became negative the following day, but the signs of meningitis persisted. At autopsy there was a purulent leptomeningitis and also a purulent exudate over the right pleura. Culture from the blood, pleura and meninges showed streptococcus and *Staphylococcus aureus*.

Glycosuria in meningococcic meningitis has been reported in four cases by Cole,<sup>7</sup> in three cases by Box and Nicholson,<sup>8</sup> and in one case each by Bruce and Flexner,<sup>9</sup> Ward and Driver,<sup>10</sup> Hunter<sup>11</sup> and MacNally.<sup>12</sup> Cole<sup>7</sup> observed four cases of coma with glycosuria and ketosis in a series of 20 cases of meningococcal meningitis. Two of the patients were previously known to have suffered from diabetes. In one of these Cole thought that a diabetic coma had been precipitated by the infection. In the second, treatment was instituted for diabetic coma before the existence of meningitis had been suspected. In Cole's other two cases glycosuria and ketosis occurred as a transient phenomenon at the onset of the meningitis and had entirely disappeared in four days. Each patient had a normal sugar tolerance test after the meningitis had been cured. The patients of Box and Nicholson<sup>8</sup> were children, two of whom had transient glycosuria during the first three days of a fatal meningitis. In the other, sugar appeared in the urine during a fatal relapse with hydrocephalus. In the single case reported by Ward and Driver<sup>10</sup> the patient was seen initially in coma with only minimal signs of meningeal irritation, but with glycosuria and ketosis. A diagnosis of diabetic coma was made and during the first 5 hours 110 units of insulin and 1,500 c.c. of 2.5 per cent glucose in saline were given. Three hours after the last insulin had been given the blood sugar was 190 mg. per cent. He rapidly recovered consciousness and then for the first time was recognized

to have signs of meningitis. This was confirmed by lumbar puncture and treated by sulfapyridine with complete recovery. A glucose tolerance test performed prior to his discharge from the hospital showed a normal curve with no glycosuria. Hunter's case presented a similar story of coma accompanied by acetone breath and by sugar and acetone in the urine. Insulin was administered and the urine was thereafter free of sugar and ketones. It was after the treatment of supposed diabetes was complete that signs of meningeal involvement were first recognized. Treatment of the infection with sulfapyridine led to complete recovery. Sugar tolerance after discharge from the hospital was normal and there were no residual signs of diabetes.

Our cases and those in the literature fall into two categories: (1) diabetes in whom meningitis appeared as an incident (cases 1 and 2 of Cole's series and our case 15), and (2) previously healthy individuals in whom glycosuria appeared as a transient phenomenon at the onset of meningitis. In the first group marked glycosuria and ketosis were to be expected since it is well known that infection in diabetes may exaggerate glycosuria and ketosis or precipitate coma.<sup>13, 14</sup> In the other group the situation is not so clear. It appears unlikely that all of those who had sugar in the urine were prediabetic because their number is so much greater than would be expected from the known incidence of diabetes. Moreover transient glycosuria, hyperglycemia and diminished sugar tolerance have been demonstrated in the course of many acute infections,<sup>15</sup> and it seems not unlikely that the high incidence of glycosuria at the onset of meningitis may be only an exaggerated response to a sudden infection of great severity. The accumulated data furnish no evidence to support any one of the various theories for glycosuria in infections such as depression in insular function,<sup>15</sup> inhibition of the action of insulin,<sup>16, 17, 18</sup> or excessive hepatic glycogenolysis.<sup>19, 20, 21</sup> It is also possible, as has been suggested frequently in the literature<sup>4, 6, 10</sup> that the glycosuria is in part attributable to increased intracranial pressure or actual involvement of nerve structures about the fourth ventricle and is similar in mechanism to the *piqûre* diabetes of Claude Bernard. Perhaps pertinent is the incidence of cranial nerve paralyzes in cases of meningitis which have exhibited glycosuria. In the cases of Taylor and McKinstry,<sup>6</sup> Roussel,<sup>5</sup> Ward and Driver,<sup>10</sup> McNally<sup>12</sup> and Cole<sup>7</sup> nerve defects ranging from lateral rectus palsies to complete hemipareses were reported. Among our 16 cases there were at least three definite nerve paralyzes. It should be noted, however, in our case 10 and in the reports of Ward and Driver<sup>10</sup> and Hunter<sup>11</sup> glycosuria and ketosis appeared early in the infection before there was any clinical evidence of meningeal involvement. Our data offer no evidence upon such possible mechanisms as depression of insular function.

The fact that glycosuria disappeared promptly following the administration of insulin in some of the cases cannot be used as evidence for or against insulin resistance as a cause since similar prompt recoveries of normal carbohydrate relationships occurred in several cases to which no insulin was given.

From a practical standpoint the most important aspect of glycosuria in meningitis is the possibility that the occurrence of coma with glycosuria, hyperglycemia, and ketosis at the onset of the infection may lead to a diagnosis of diabetic acidosis and that in the meantime the signs of meningitis may be masked or missed entirely. In the cases reported by Ward and Driver<sup>10</sup> and by Hunter<sup>11</sup> glycosuria and other signs indicating disturbed carbohydrate relationships preceded the signs of meningitis and in our case 10 were evident before the spinal fluid had become abnormal. In Cole's second fatal case the initial coma with glycosuria, hyperglycemia and ketosis was diagnosed and managed as diabetic coma for 24 hours before the meningitis was recognized or given the benefit of sulfonamide drugs.

### SUMMARY

1. Spontaneous glycosuria occurs frequently at the onset of meningitis. It appeared in 16 of 72 consecutive cases of meningitis and in over one third of 26 cases of meningococcic meningitis.

2. It was encountered in meningitis caused by the meningococcus, the pneumococcus, the staphylococcus, the tubercle bacillus and in one case in which the causative organism was not isolated.

3. Glycosuria was accompanied in many instances by ketosis, hyperglycemia and diminished tolerance to sugar.

4. Glycosuria was transient, disappeared in all cases and persisted beyond the third day in only three of the 16 cases.

5. Coma with glycosuria and ketosis at the onset of meningitis may mask the signs of meningeal involvement, lead to a diagnosis of diabetic acidosis and cause serious or fatal delay in instituting appropriate treatment for the meningitis.

### BIBLIOGRAPHY

1. LOEB, M.: Ein Erklärungsversuch der verschiedenartigen Temperaturverhältnisse bei der tuberculösen Basilmeningitis, *Deutsch. Arch. f. klin. Med.*, 1884, xxxiv, 443.
2. FREW, R. S., and GARROD, A. E.: Glycosuria in tuberculous meningitis, *Lancet*, 1913, i, 15.
3. NOHECOURT, P.: Syndrome de vomissements avec acetonurie au debut des meningites a meningocoques et des meningites tuberculeuses, *Prog. Med.*, 1933, i, 110.
4. KRAFCHIK, L. L., and SLOBODY, L. B.: Tuberculous meningitis resembling diabetic coma, *Arch. Pediat.*, 1938, iv, 288.
5. ROUSSEL, A. E.: Pneumococcus meningitis simulating diabetic coma with recovery, *Atlantic Med. Jr.*, 1926, xxx, 159.
6. TAYLOR, F. E., and MCKINSTY, W. H.: A case of suppurative meningitis with glycosuria simulating diabetic coma, *Lancet*, 1917, i, 182.
7. COLE, L.: Diagnosis of coma in cerebrospinal fever with diabetes, *Lancet*, 1942, ii, 421.
8. BOX, C. R., and NICHOLSON, T. G.: The glycosuria associated with meningitis, *Lancet*, 1917, i, 239.
9. BRUCE, J. W., and FLEXNER, M.: Meningococcus meningitis: report of an unusual case, *Arch. Pediat.*, 1926, xliii, 473.
10. WARD, C. W., and DRIVER, A. A.: Meningococcal meningitis starting as diabetic coma, *Lancet*, 1940, ii, 228.



11. HUNTER, R. R.: Glycosuria in meningococcal meningitis, *Lancet*, 1940, ii, 604.
12. McNALLY, W. D.: Meningitis with a diabetic coma, *Illinois Med. Jr.*, 1941, lxxx, 507.
13. GREENE, J. A., and KEOHEN, G. F.: Insulin resistance due to infection in diabetes mellitus in man, *Jr. Am. Med. Assoc.*, 1943, cxxi, 173.
14. GREENE, J. A., DAVID, A., and JOHNSTON, G.: Production of insulin resistance in depancreatized dogs, *Am. Jr. Physiol.*, 1942, cxxxvi, 595.
15. WILLIAMS, J. L., and DICK, G. F.: Decreased dextrose tolerance in acute infectious diseases, *Arch. Int. Med.*, 1932, 1, 801.
16. SWEENEY, J. S., and LACKEY, R. W.: The effect of toxemia on tolerance for dextrose, *Arch. Int. Med.*, 1928, xli, 257.
17. SWEENEY, J. S., BARSHOP, N., and LEBELLO, L. C.: Effect of toxemia on tolerance for dextrose and on the action of insulin, *Arch. Int. Med.*, 1934, liii, 689.
18. SWEENEY, J. S., BARSHOP, N., LEBELLO, L. C., and ROSENTHAL, R. S.: Effect of toxemia on the tolerance for dextrose and on the action of insulin, *Arch. Int. Med.*, 1934, liv, 381.
19. SOSKIN, S., ALLWEISS, M. D., and MIRSKY, I. A.: Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function, *Arch. Int. Med.*, 1935, lvi, 927.
20. SOSKIN, S., and MIRSKY, I. A.: The influence of progressive toxic liver damage upon the dextrose tolerance curve, *Am. Jr. Physiol.*, 1935, cxii, 649.
21. MIRSKY, I. A.: The etiology of diabetic acidosis, *Jr. Am. Med. Assoc.*, 1942, cxviii, 690.

# THE WATERHOUSE-FRIDERICHSEN SYNDROME: OBSERVATIONS ON ASSOCIATED ADRENAL INSUFFICIENCY AND REPORT OF FOUR CASES\*

By STUART W. COSGRIFF, M.D., *New York, N. Y.*

## INTRODUCTION

WITH the recent increase in prevalence of meningococcal meningitis, there has been, as might be anticipated, an associated rise in the number of cases of the so-called Waterhouse-Friderichsen syndrome.<sup>1, 2</sup> This condition, characterized by shock, purpura and hemorrhages into the adrenal glands, is encountered in overwhelming sepsis resulting as a rule from meningococcus infection, but it may also be due to any one of a variety of organisms.<sup>3, 4, 5</sup> Because this symptom complex has been described infrequently in the past, it becomes of interest to review this disorder with particular emphasis on possible relationships of adrenal insufficiency to the underlying mechanisms of the syndrome. In the past eight months, four adult patients with the Waterhouse-Friderichsen syndrome were admitted to the Presbyterian Hospital. In two of these, detailed studies pertaining to abnormalities of electrolytes, sugar, and non-protein nitrogen in the blood were carried out. In addition, the possible therapeutic value of various adrenal cortical substances and fluids was observed. The data obtained and the results of such therapy are presented in this report.

## DISEASE PICTURE

A review of the literature, with slightly more than 100 cases recorded, indicates that the Waterhouse-Friderichsen syndrome is more common in children, the majority of patients being less than two years of age, 90 per cent occurring in children under 10 years, and both sexes being equally affected.<sup>3, 4, 5</sup> The onset is characteristically rapid, often with prodromal malaise, chills, fever, and joint pains. In a matter of a few hours, signs of marked prostration appear, petechiae and purpura become evident, and areas of blotchy cyanosis are seen. The patient becomes rapidly stuporous or comatose, with progressive peripheral circulatory collapse, and death usually occurs within 12 to 36 hours after onset.

Physical examination usually shows a desperately ill patient, with variable but often high fever, weak or imperceptible pulse, and blood pressure too low to be determined. An extensive purpuric rash appears, and conjunctival hemorrhages may result in the unusual manifestation of "bloody

\* Received for publication July 30, 1943.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

This work was done prior to induction into military service.

tears." Profound and variable cyanosis is usually present. Clinical evidence of meningeal irritation is either minimal or absent, probably because the rapid fulminating course does not allow time for extensive meningeal infection to take place. Pains in the extremities and joints may cause great distress.

Detailed laboratory studies are infrequently recorded, because of the rapid course of the disease process. Data are available to indicate that, in cases resulting from meningococcemia, a mild to moderate polymorphonuclear leukocytosis is the rule, with a tendency to thrombocytopenia. Despite the purpuric and thrombocytopenic tendency, tests of capillary fragility have not been reported. In a few cases, there has been found an elevated non-protein nitrogen and a lowered blood sugar.<sup>4, 5, 6, 7</sup> The spinal fluid is characteristically normal, and culture of the spinal fluid is usually negative. Blood cultures are usually positive.

TABLE I

Chemical Changes in the Blood in Two Cases of the Waterhouse-Friderichsen Syndrome

Name	Urea Nitrogen	Sugar	Sodium	Protein	Chlorides	CO <sub>2</sub>
	mg. per 100 c.c.	mg. per 100 c.c.	m. eq. per l.	Grams per 100 c.c.	m. eq. per l.	m. eq. per l.
S. M. Case 1	58	50	127.9 122.9	6.2	95.4	17.5
J. B. Case 2	26	245	128.6	7.2	100	18.6

At autopsy, the principal findings are the invariable hemorrhages into the adrenal glands, and frequently into the skin, muscles, brain and other organs. Focal myocarditis, focal necroses of the liver, and acute splenic tumor are often present.

An accurate antemortem diagnosis is difficult and infrequent. The syndrome may readily be confused with the onset of many infectious processes. In many instances, the picture is not unlike that produced by a blood dyscrasia, such as acute leukemia or a crisis in thrombocytopenic purpura. Acute rheumatic fever may be suggested by the joint complaints. Other cases resemble acute poisoning or heart failure, by virtue of the cyanosis, collapse, and respiratory difficulty. The comatose condition may be confused with cerebral accidents or uremia. The skin rash needs to be distinguished from that of the rickettsial diseases.

#### CASE REPORTS

*Case 1.* S. M., a 32 year old white American housewife, was in perfect health until 30 hours before admission, when she was awakened during the night by a shaking chill lasting one hour. Temperature was subsequently found to be 105° F. by mouth, and after several hours she complained of generalized aches most marked in the extremities. A skin eruption was then observed on her arms and legs. A

physician was called, and administered antipyretics with subsequent drop in temperature to normal. Because of increasing prostration, more severe aches and spreading skin lesions, hospital admission was advised.

On admission, the patient appeared acutely ill and cyanotic with a rectal temperature of 98° F. She was pulseless; and the blood pressure could not be obtained. Her heart rate was 140. A purpuric rash varying from petechial hemorrhages to large ecchymotic areas was scattered over the entire body. Bilateral conjunctival hemorrhages were present. There were no signs of meningeal irritation, and the remainder of the examination showed no abnormalities.

Laboratory tests: The blood showed 14 grams of hemoglobin, the red cell count 3,870,000, leukocytes 17,000 with 56 per cent polymorphonuclears and a marked shift to the left. Platelets were 32,000. The capillary resistance, as measured by the negative pressure suction pump, was normal on admission: no petechiae were observed with a pressure of minus 30 mm. of mercury exerted for one minute. Thirty hours later, petechiae were observed at a pressure of minus 20 mm. of mercury for one minute. The hematocrit was 48.6 per cent, and the sedimentation rate was 25 mm. in one hour. Urinalysis showed a three plus albuminuria, and occasional red and white blood cells. Lumbar puncture produced crystal clear fluid with a pressure of 170 mm. of water, containing 2 cells per cu. mm., protein 63 mg. per cent, sugar 64 mg. per cent, and culture gave no growth. The serum proteins were 6.2 grams per cent, the serum CO<sub>2</sub> 17.5 milli-equivalents per liter, serum chlorides 95.4 milli-equivalents per liter, the serum sodium 127.9 milli-equivalents per liter on one occasion and 122.9 milli-equivalents per liter on another determination, urea nitrogen 58 mg. per cent, serum sugar 50 mg. per cent.

Course: On admission, the diagnosis of meningococcemia with the Waterhouse-Friderichsen syndrome was suspected. Throughout her course, the temperature varied from 97.4 to 99.4° F. by rectum. The admission blood culture was subsequently found to contain meningococci. On admission, she was immediately given an infusion of 2,000 c.c. of 5 per cent glucose in saline, containing five grams of sodium sulfadiazine. She also received a blood transfusion of 500 c.c. Six hours later, a blood pressure of 60 mm. Hg systolic and 40 mm. diastolic was obtained, and the radial pulse became palpable. In the course of the next three days, she received a total of 20 milligrams of desoxycorticosterone acetate,\* 140 c.c. of Upjohn's cortical extract, 50 c.c. of eschatin, and further saline and glucose infusions. During this period, blood pressure varied from 70 mm. Hg systolic and 40 mm. diastolic to 110 mm. systolic and 74 mm. diastolic, and the patient became somewhat more alert. Further parenteral sodium sulfadiazine maintained the daily blood levels between 16 and 18 mg. per cent. With no new significant findings, death occurred suddenly 72 hours after admission.

Autopsy showed the hemorrhagic skin and mucous membrane lesions noted clinically. In addition, there was an acute fibrinous pericarditis and acute focal myocarditis. The adrenal glands were of normal size, but 80 to 90 per cent of the glands were grossly hemorrhagic, and histologically almost the entire cellular structure of both cortex and medulla was obliterated by extravasated red blood cells. No examination of the central nervous system was permitted.

Case 2. J. B., a 16 year old white schoolboy, who gave a history of a mild upper respiratory infection for the preceding week, suddenly felt ill 10 hours before admission. He developed a shaking chill and fever to 105° F., and eight hours later was found comatose at home. His physician was summoned, who found his temperature to be 109° F. (?). He was then transported by ambulance to the Presbyterian Hospital.

\* Supplied through the courtesy of Roche-Organon, Inc., Nutley, New Jersey.

On admission, the patient appeared acutely ill, cyanotic, and comatose. Rectal temperature was 106° F., pulse was 130 weak, respirations 30, and blood pressure was 80 mm. Hg systolic and 55 mm. diastolic. A generalized petechial eruption with scattered areas of purpura was present. There were hemorrhagic tears. There was generalized rigidity, neck flexion was somewhat resistant, and the Kernig test was positive. The remainder of the examination was normal.

Laboratory tests: The blood showed 14.3 grams of hemoglobin, the red cell count 5,200,000, the leukocytes 12,000 with 90 per cent polymorphonuclears and a marked shift to the left on admission (later rising to 32,000). The platelets were 121,000. The sedimentation rate was 13 mm. in one hour. No urine was obtained. Lumbar puncture produced crystal clear fluid with a pressure of 128 mm. of water, containing 8 cells per cu. mm., protein 23 mg. per cent, sugar 120 mg. per cent, and culture was negative. The serum urea nitrogen was 26 mg. per cent, serum sugar 245 mg. per cent, serum proteins 7.2 grams per cent, serum CO<sub>2</sub> 18.6 milli-equivalents per liter, serum chlorides 100 milli-equivalents per liter, serum sodium 128.6 milli-equivalents per liter. The blood culture taken on admission was positive for meningococci, but nose and throat cultures were negative.

Course: On admission, it was felt that the patient had a sepsis, associated with a possible Waterhouse-Friderichsen syndrome. He was promptly given 2000 c.c. of intravenous saline and glucose containing seven grams of sodium sulfadiazine, a whole blood transfusion of 500 c.c., and 50 c.c. of eschatin. Despite the above, however, his temperature remained elevated, and he grew steadily worse. He became cyanotic with irregular respirations, developed a progressively weaker pulse, and blood pressure dropped to 70 mm. Hg systolic and 20 mm. diastolic. The patient died 29 hours after the onset of his disease.

Autopsy revealed the petechial and hemorrhagic lesions widespread throughout skin, muscles and mucous membranes. There were focal necroses of the liver. The meninges and the brain were normal. The adrenals were grossly normal, but microscopically showed extensive edema and hemorrhage of the capsule. There were only a small number of hemorrhagic extravasations into the cortical tissue. The medulla of the glands was normal, save for a moderate polymorphonuclear infiltration.

*Case 3.* E. A., a 71 year old housewife, was known to have had a mild hypertension for 15 years, but was in good health until 20 hours before admission. When awakened from her usual noonday rest, she was confused and complained of weakness in her left arm and leg. Her physician was summoned, and on his arrival within an hour found her to be comatose, and her oral temperature 105° F. He considered the patient to have had a cerebral accident, and administered antipyretics without avail. During that evening her temperature rose to 106° F., generalized purpura appeared, and she was brought to the hospital by ambulance.

On admission, the patient was obviously in extremis, comatose, and cyanotic. Respirations were gasping and irregular. Generalized purpura was present. Temperature was not taken; blood pressure was 55 mm. Hg systolic and 50 mm. diastolic; pulse was imperceptible. The heart rate was 120. The pupils were fixed, but the neck was supple. The remainder of the examination was not remarkable.

The patient was felt to have had a cerebral accident. Because of her cyanosis, she was placed in oxygen, but died one-half hour after admission.

At autopsy, the generalized hemorrhages as noted clinically were prominent. There was an acute interstitial myocarditis. The adrenal glands were of normal size, but signs of gross hemorrhage extended throughout each gland. Histological examination revealed that widespread red blood cell extravasations obscured the architecture of most of the cortex. Those cortical cells in the portion of the gland with normal architecture showed no evidence of toxic necrosis. The brain and meninges showed no signs of recent vascular thrombosis, hemorrhage, or inflammation.

*Case 4.* S. S., a 47 year old housewife, was perfectly well until 24 hours before admission, when she complained of malaise and found her temperature to be 102° F. by mouth. The physician who attended her made a diagnosis of "grippe." Twelve hours later during the evening, she noted a rash appearing over her entire body, and experienced some difficulty in breathing. She complained bitterly of pains in her arms and legs, and said that they felt paralyzed. Five hours before admission, she began having greater respiratory difficulty, and her husband noted that she was becoming blue. Her temperature was 104° F. by mouth. She was given oxygen for several hours at home, and then was transported by ambulance to the Presbyterian Hospital.

On admission, she was comatose, cyanotic, and extremely dyspneic. Petechiae were scattered sparsely over the buccal membranes and the extremities. The conjunctivae were hemorrhagic, and there were "bloody tears." Pulse was imperceptible; the heart rate was rapid. Despite oxygen and stimulants, she died five minutes after admission. Blood cultures, as well as those of nose and throat, were later reported as positive for meningococci.

Autopsy revealed the generalized hemorrhages of the skin, subcutaneous tissues, muscles, heart, intestines, and especially of the adrenal glands. The adrenals were of normal size and shape. The whole substance of the gland was grossly hemorrhagic. Histologically, the usual architecture was replaced by massive extravasations of red blood cells. The brain and meninges were normal.

#### DISCUSSION

The Waterhouse-Friderichsen syndrome has been reviewed on previous occasions.<sup>3, 4, 5, 7, 8, 9</sup> But with 806 cases of meningococcus meningitis reported in New York City during the first five months of 1943 as compared to 48 cases in a similar period in 1941, it is fair to expect that an increase in the Waterhouse-Friderichsen cases will occur. This is suggested by the admission of four patients with this disorder, described as being much more common in childhood, to the adult wards of Presbyterian Hospital during the eight-month period ending April 1943. As diagnosis is difficult and therapy of little avail unless the initial sepsis can be rapidly overcome, the early recognition of this disease assumes increasing importance.

The question has often been raised as to the rôle of the adrenal glands in the production of this syndrome. Adrenal cortical insufficiency is suggested by: (1) the clinical pattern of hypotension, dehydration, and vomiting; (2) the laboratory findings of lowered blood sodium in our patients, an elevated non-protein nitrogen occasionally associated with hypoglycemia; and (3) the pathologic finding of hemorrhagic damage to the adrenal glands.

On the other hand, the clinical picture described above, although consistent with a diagnosis of hypoadrenalism, is not specific for this condition, and may be the result of overwhelming infection with generalized tissue damage. Furthermore, as brought out by the autopsy findings in the second case reported in this paper, the extent of adrenal cortical destruction may be small in the Waterhouse-Friderichsen syndrome; and it is well known that only a small portion of the adrenal cortex need remain for the preservation of normal function in the experimental animal. Although there are a

small number of patients seen in an Addisonian crisis who fail to respond to specific treatment, the majority of patients react favorably to the administration of fluids, electrolytes, and adrenal cortical replacement therapy.<sup>10</sup> The lack of response in the first two cases reported here may be an added argument that hypoadrenalism is not the primary cause of death, but is conceivably a contributing factor.

Recent studies indicate an increase in the urinary excretion of hormonal substances, presumably of adrenal origin, in infections as well as in severe burns and postoperative states.<sup>11</sup> For these reasons, the possible rôle of the adrenal glands should not be disregarded, since in the presence of severe infection, varying degrees of hypoadrenalism, if untreated, may be sufficient to precipitate a fatal outcome. It may be that if adequate supportive adrenal therapy is administered, such therapy may successfully bolster a seriously embarrassed body economy. This replacement therapy should be conducted along such lines as suggested by Loeb in the discussion of the therapy of an Addisonian crisis.<sup>10, 12</sup> Recently there have been reported three cases which were clinically the Waterhouse-Friderichsen syndrome, and which recovered following active treatment along the general program of combating both the septicemia and the possible adrenal disturbance.<sup>13, 14, 15</sup>

Acute and overwhelming septicemia initiates the disease resulting in the Waterhouse-Friderichsen syndrome, and therefore constitutes the first therapeutic consideration.<sup>16</sup> Rapid and adequate chemotherapy is the accepted means of combating the blood stream infection. Sulfadiazine is generally considered to be the most effective and least toxic sulfonamide in these cases, and it should be administered by intravenous and subcutaneous methods as well as the usual oral route. Adequate and possibly high sulfadiazine blood levels should be maintained in the presence of such a severe process. Unless the infection is overcome, even the most successful therapy of the possible adrenal insufficiency would be of no avail.

Inasmuch as many of the organisms responsible for this syndrome are known to be highly susceptible to the antibacterial action of penicillin,<sup>17, 18</sup> and as this agent exerts its effect against the offending organisms without the usual lag phase observed with the sulfonamides,<sup>19</sup> it is possible that penicillin or related substances may prove to be even more potent therapeutic weapons in combating this type of sepsis.

#### SUMMARY

1. Four cases of the Waterhouse-Friderichsen syndrome in adults are reported.
2. In two patients in whom analyses were made, a decrease in the serum sodium and an increase in the non-protein nitrogen compatible with adrenal-cortical insufficiency were encountered.
3. These changes bore no relationship to the extent of damage observed in the adrenal cortex at autopsy.

4. The rôle of hypoadrenalism in the mechanism of this syndrome is not as yet established.

5. Therapy should be directed primarily towards the treatment of sepsis, and secondarily towards the correction of possible associated adrenal cortical insufficiency.

## BIBLIOGRAPHY

1. WATERHOUSE, R.: A case of suprarenal apoplexy, *Lancet*, 1911, i, 576.
2. FRIDERICHSEN, C.: Nebennierenapoplexie bei kleinen Kindern, *Jahrb. f. Kinderh.*, 1918, lxxxvii, 109.
3. AEGERTER, E. E.: The Waterhouse-Friderichsen syndrome; a review of the literature and a report of two cases, *Jr. Am. Med. Assoc.*, 1936, cvi, 1715.
4. KUNSTADER, R.: The Waterhouse-Friderichsen syndrome, *Arch. Pediat.*, 1939, lvi, 489.
5. SACKS, M.: Fulminating septicemia associated with purpura and bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome); report of 2 cases with review of the literature, *ANN. INT. MED.*, 1937, x, 1105.
6. MAGNUSSON, J. H.: Contribution to the knowledge of acute suprarenal insufficiency in children, *Acta paediat.*, 1934, xv, 396.
7. LINDSAY, J. W., RICE, E. C., SELINGER, M. A., and ROBIN L.: The Waterhouse-Friderichsen syndrome, *Am. Jr. Med. Sci.*, 1941, cci, 263.
8. MONFORT, J. A., and MEHRLING, J. H.: The Waterhouse-Friderichsen syndrome, *Am. Jr. Dis. Child.*, 1941, lxii, 144.
9. MICHAEL, P., and JACOBUS, L.: The Waterhouse-Friderichsen syndrome, *Arch. Pediat.*, 1942, lix, 141.
10. LOEB, R. F.: The adrenal cortex and electrolyte balance, *Bull. New York Acad. Med.*, 1942, xviii, 263.
11. WEIL, P., and BROWN, J.: A cortin-like action of extracts of human urine, *Am. Jr. Physiol.*, 1939, cxxvi, 652.
12. LOEB, R. F.: Diseases of the adrenals, 1943, Oxford University Press, New York, p. 783.
13. GRACE, W. A., HARRISON, C. V., and DAVIE, T. B.: Suprarenal hemorrhage in meningococcal septicemia, *Lancet*, 1940, ii, 102.
14. CAREY, T. N.: Adrenal hemorrhage with purpura and septicemia (Waterhouse-Friderichsen syndrome) with recovery; case report, *ANN. INT. MED.*, 1940, xiii, 1740.
15. RUCHS, W., and HOBSON, J.: Purpura fulminans (Waterhouse-Friderichsen syndrome), *Jr. Pediat.*, 1943, xxii, 226.
16. FINLAND, M., and DINGLE, J.: Diagnosis, treatment and prevention of meningococcal meningitis, *War Med.*, 1942, ii, 1.
17. CHAIN, E., FLOREY, H. W., GARDENER, A. D., HEATLEY, N. G., JENNINGS, M. A., ORR-EWING, J., and SANDERS, A. G.: Penicillin as a chemotherapeutic agent, *Lancet*, 1940, ii, 226.
18. HERRELL, W. E.: Further observations on the clinical use of penicillin, *Proc. Staff Meet. Mayo Clin.*, 1943, xviii, 65.
19. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Mechanism of action of penicillin, *Proc. Soc. Exper. Biol. and Med.*, 1942, 1, 281.



# MENINGOCOCCIC MENINGITIS—SULFADIAZINE THERAPY (REVIEW OF TWENTY CASES)\*†

By EMIL H. GRIECO, Captain, M.C., A.U.S., and ARTHUR M. COVE, Captain, M.C., A.U.S., *Fort Totten, New York*

## INTRODUCTION

AN increased occurrence of all types of contagious diseases may be anticipated incidental to the mobilization of large groups of men. During the year 1941, no cases of epidemic meningitis were seen in this institution, whereas from June 1942 through June 1943, 20 cases of this disease were treated here (Station Hospital, Fort Totten, New York). These cases were sporadic throughout the metropolitan area. Their scatter precluded epidemic consideration. No direct contact had been established between any two of this group of patients. Routine pharyngeal cultures of the men comprising the groups from which these cases had been isolated disclosed but five carriers. In none of these was the recovered meningococcus similar in type to that found in the men with active disease.

Favorable reports abound in the literature concerning the use of sulfanilamide and its derivatives, in the treatment of meningococcic meningitis.<sup>1, 2, 3, 4, 5, 6</sup> Sulfadiazine and its soluble sodium salt was the only sulfonamide utilized in the management of the 20 consecutive cases reported here. In one of our earliest cases, polyvalent anti-meningococcic serum was administered intravenously in conjunction with chemotherapy. Such a severe reaction ensued that we abandoned the use of serum thereafter. The plan of treatment conformed in general to that outlined in S.G.O. Circular Letter No. 17.<sup>7</sup>

## CLINICAL FEATURES

The prodromal period in the majority of patients was brief, rarely exceeding two to three days, and was characterized in the main by mild sore throat, chills and fever, headache, nausea and vomiting. In two instances, the patients were found unconscious in bed, with no history of preceding illness or disability.

Headache, present in practically all cases, was a most distressing complaint. It was generally described as throbbing or pounding, and diffuse in character. This symptom, difficult to relieve, practically paralleled the clinical response of the patient—as the latter improved, the former lessened. Nausea and vomiting were frequent concomitants of this symptom. Nuchal rigidity of varying grades of severity, found in nearly all cases, lasted on an average from four to five days.

\* Received for publication November 1, 1943.

† The authors wish to express their appreciation to Colonel A. J. Vadala, M. C., for his kind assistance in the preparation of this paper.

In slightly more than half, the classical, full-blown picture of meningitis (marked nuchal rigidity, stupor or active delirium, positive Kernig sign, absent abdominal reflexes, etc.) presented itself. The remainder, although not so severe, offered no difficulties in diagnosis.

Various levels of depression, ranging from mild somnolence to lethargy, usually accompanied by motor restlessness, were fairly common. Ocular signs, strabismus, nystagmus, oculogyric movements, were noted in three cases.

Cutaneous lesions, seen in 11 patients, were principally petechial in nature, located predominantly over the anterior abdomen and extremities. Two patients manifested purpuric eruptions. One had varying sized coalescent, well demarcated areas of hemorrhage over the forehead, body, and extremities. Massive hemorrhagic extravasations occurred in both lower extremities up to the knees. Reactive edema caused the facies to assume a bloated appearance, and the legs to enlarge twice their normal size. The involved skin areas became anesthetic, underwent a dry necrosis, and formed hard, black eschars. This patient exhibited the clinical picture of the so-called Waterhouse-Friderichsen syndrome, and survived his illness.

#### LABORATORY STUDIES

A polynucleosis of the peripheral blood was a universal finding. The total white blood cell counts ranged from 16,300 to 39,800.

The gross appearance of samples of cerebrospinal fluid obtained on initial puncture varied from slight turbidity to cloudiness. Stained smears of the sediment after centrifugation, yielded a gram-negative intracellular diplococcus in 17 (85 per cent) instances. Successful cultures were obtained in 15 (75 per cent) cases.\* "It is important to remember that meningococci in spinal fluid undergo solution very readily, a solution which is probably an autolysis with the result that spinal fluid which may be full of polys contains very few recognizable organisms. This readiness to go into solution may cause problems in cultivation."<sup>8</sup>

The relatively large number of successful cultures in this series is, we feel, due to the practice of early spinal puncture, and the ready institution of culturing procedures. These steps will lessen the number of unsuccessful implants.

Blood cultures of venous blood, withdrawn within a few hours or less of admission, were positive in seven (35 per cent) patients. It is of interest to note that five of these were from patients with cutaneous lesions, as could be anticipated.

Immunologically, of the 15 positive recoveries of the meningococcus by culture, 13 and 2 were demonstrated to be of the epidemic strains Type I and Type II, respectively.\*

\* Second Service Command Army Laboratories.

## MANAGEMENT

Diagnostic tap was done on all suspected cases upon admission. Unless some indication warranted it, e.g. signs of block, failure to respond to therapy, etc., this procedure was not repeated. Blood for culture was obtained from all at the same time.

As soon as the diagnosis was verified, an initial dose of 5 grams of sodium sulfadiazine in 100 c.c. of distilled water was administered intravenously; this latter, even though the patient could take the drug orally. Subsequent doses of 2 grams were then given regularly every four hours for the next 24 hours, either orally or intravenously, as determined by the patient's ability to ingest or retain the medication. The oral route was substituted in all those receiving intravenous therapy as soon as the clinical condition permitted. One gram doses every four hours until the temperature returned to normal, and from this point on four times daily for the next seven days, was the course then pursued.

During the acute phase of the disease, blood sulfä levels were determined daily, and upon amelioration, every other day. Complete blood counts and urinalyses were done routinely every other day so long as chemotherapy was employed.

It was the general policy not to administer parenteral fluids unless necessary. This group of young and robust males was not affected adversely by slight or moderate degrees of dehydration. So long as a urinary output of 750 c.c. or more was obtained during the first 24 hours, no parenteral fluids were employed. It was found that an adequate urinary excretion could be attained by fluids taken orally if frequently administered. In but three patients was it necessary to resort to the use of intravenous fluids for short intervals because of vomiting.

The sedation of delirious and restless patients was fairly well maintained by the intramuscular injection of paraldehyde in quantities of 5 to 10 c.c. This dose could, upon necessity, be safely repeated within several hours. On a few occasions the drug was administered intravenously with good results. "This drug possesses a wide margin of safety. Very large doses cause only prolonged unconsciousness, fatalities being quite rare."<sup>9</sup>

The sudden development of hypotension, feeble pulse, marked asthenia, and semi-stupor, marked the clinical deterioration of one patient (case 17). The blood pressure dropped to 70 mm. of Hg systolic and 40 mm. diastolic (mercurial manometer). Aqueous adrenal cortical extract was given intramuscularly in conjunction with physiologic saline solution intravenously. The blood pressure slowly rose to 110 mm. systolic, 50 mm. diastolic; 114 mm. systolic, 52 mm. diastolic; and 112 mm. systolic, 60 mm. diastolic. By the third day, clinical improvement was definite and progressive. All in all, 65 c.c. of extract were given.

Marked bladder atony necessitated the use of an indwelling catheter for a period of seven days before spontaneous urination was resumed in this patient.

TABLE I  
Summary of 20 Cases

Summary of 20 Cases																					
Lab. Data										Clinical Course											
Case No.	Age	Spinal Fluid				Drug		Lab. Data						Clinical Course							
		Turbidity	Smear	Culture, Gr.	Punctures, No.	Quantity, Gr.	Blood Level	Duration, Days	Reactions	Bl. Cult. Gr.	W.B.C.	Urine	Serology	Pharyn. Cult.	Temp. High	Temp. Days	Hosp. Days No.	Severity	Complication	Sequelae	Disposition
1	22	++	+	I	1	66	15	12	—	—	17,100	—	—	—	102	2	24	++		none	duty
2	28	+	—	—	1	83	10	10	—	—	16,300	—	—	—	101	2	20	+		none	duty
3	34	++	+	—	3a	45	13.1	5	—	—	29,350	—	—	—	103	6	66	++	+d	none	duty
4	33	++	+	II	1	50	8.4	8	—	—	29,800	—	—	—	102.2	1	23	++		none	duty
5	39	++	+	—	1	39		7	—	—	21,250	—	—	—	105	3	28	++		none	duty
6	26	++	+	I	1	5		(fulminating case—died within 12 hours)													death
7	20	++	+	I	2	40*	25.7	4	I	24,500	rbc	—	—	—	103.4	4	4	++	+c	none	autopsy
8	21	++	+	I	3	41	10.2	6	—	37,250	—	—	—	—	101.8	2	7	++	+f	none	duty
9	19	++	+	I	1	62	9.1	9	—	27,400	rbc	—	—	—	104	3	23	++		none	duty
10	32	++	+	I	2	46	21	13	I	28,400	rbc	—	—	—	104	5	17	++		none	duty
11	23	++	+	—	1	46	7	8	—	21,600	—	—	—	—	103.5	2	12	++		none	duty
12	39	++	+	I	1	80	21	13	I	32,500	—	—	—	—	103	3	19	++		none	duty
13	31	++	+	—	2	53	17	9	—	32,600	—	—	—	—	103.6	3	21	++		none	duty
14	24	++	+	I	1	40	3	10	—	22,750	rbc	—	—	—	100.6	3	13	+		none	duty
15	31	++	+	I	1	40	5	8	—	18,700	—	—	—	—	101.2	1	12	+		none	duty
16	22	++	+	I	1	59	14	10	I	39,800	—	—	—	—	104	3	25	++	+g, h	none	duty
17 <sup>e</sup>	26	++	+	I	1	86	8	13	I	18,700	rbc	—	—	—	104	17	90	++	+i, j	none	duty
18	25	++	+	II	1	75	17	10	II	25,500	rbc	—	—	—	105.8	4	28	++		none	duty
19	28	++	+	I	1	50	6	9	—	20,100	rbc	—	—	—	102.5	2	30	++		none	duty
20	22	—	—	—	1	—	—	—	I	32,000	—	—	—	—	103.4	1	18	+		none	duty

\* Serum administered and discontinued.

a Suspected block—one cisternal tap done.

b Nausea and vomiting (late in disease).

c Rash and fever.

d Motor aphasia.

e Waterhouse-Friderichsen syndrome.

f Left facial and abducens paresis.

g Patient still in hospital.

h Areas of cutaneous gangrene.

i Pyarthrosis—right knee.

j Radiculitis—right S<sub>1-5</sub>.

Of unusual interest is case 20. This patient was hospitalized because of chills, fever, petechial rash, generalized aches and pains. The cerebrospinal fluid contained 80 cells per cu. mm. No organisms were seen on smear or recovered by culture of this fluid. All symptoms cleared up within 24 hours without chemotherapy. Blood obtained for culture on admission was later reported as positive for meningococci. This was manifestly a case of spontaneous recovery in a patient with acute meningococcemia and early cerebral irritation.

#### COMPLICATIONS, FATALITIES

Drug reactions were encountered in three patients. Jargon aphasia and motor perseveration in one, nausea and vomiting, rash and fever in two were the clinical manifestations of these reactions. Fortunately, these occurred rather late in the course of the disease, when withdrawal of the drug did not deleteriously affect the progress of the patient.

No renal complications were evidenced in this group. Microscopic hematuria was demonstrated in the admission specimens of urine obtained from seven patients. This cleared up, however, under therapy.

Pyarthrosis of the right knee occurred once. Repeated aspiration, semi-fixation, and skin traction effected a rapid response with no residual joint changes. Culture of the aspirated fluid did not yield the meningococcus. Subsequent radicular pains in the distribution of right SI-S5 may have been due to the traction employed. Gradual relief of this pain was accomplished by physiotherapy.

A left facial and abducens paresis with spontaneous regression and eventual complete cure, was seen in one case.

The apoplectic form of meningococcic cerebrospinal meningitis, or the Waterhouse-Friderichsen syndrome, was diagnosed clinically in one patient. Substitutional therapy, the use of adrenal cortical extract, was in this instance a life saving measure.<sup>11</sup>

Two deaths resulted in this series. One occurred within less than 12 hours after the onset of the disease; the other, four days after admission. Autopsy performed on the latter revealed a severe, bilateral, hemorrhagic necrosis of the suprarenals.\*

#### SUMMARY AND CONCLUSIONS

A review of the salient clinical features in 20 consecutive cases of meningococcic meningitis is herewith reported.

The exhibition of the drug sulfadiazine, according to the plan described, attained adequate blood concentrations, effected satisfactory clinical responses, and resulted in few complications, none of which left permanent residua.

\* Detailed report of these cases of the Waterhouse-Friderichsen syndrome to be published.

The so-called Waterhouse-Friderichsen syndrome was encountered in two patients. The survival of one of these with substitutional therapy augurs well for the outlook of this much dreaded complication.

A mortality of 10 per cent was incurred. It is felt that in a larger group of cases this percentage could be even less.

#### BIBLIOGRAPHY

1. KANTOR, H. I.: Sulfapyridine in meningococcus meningitis: review of the literature and report of a case, *New York State Jr. Med.*, 1940, xl, 1526.
2. MAIER, CONRAD: Specific treatment of epidemic meningitis with sulfanilamide derivatives (Dagenan and "Ciba 3714"), *Schweiz. med. Wchnschr.*, 1940, lxx, 879.
3. DINGLE, J. H., THOMAS, LEWIS and MORTON, A. R.: Treatment of meningococcic meningitis and meningococcemia with sulfadiazine, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2666.
4. GERNEZ, CHARLES and HURIEZ, CLAUDE: Considerations on the sulfamide treatment of the meningococcic cerebrospinal meningitis, *La presse med.*, 1941, xlix, 25.
5. FELDMAN, H. A., SWEET, L. K., and DOWLING, H. F.: Sulfadiazine therapy of purulent meningitis, including its use in twenty-four consecutive patients with meningococcic meningitis, *War Med.*, 1942, ii, 995.
6. HARRIES, G. EMRYS: Cerebrospinal fever. A review of 500 cases treated by chemotherapy without intrathecal serum, *Brit. Med. Jr.*, 1942, ii, 433.
7. S.G.O. Circular Letter No. 17, February 23, 1942, Chemotherapy in infectious diseases and other infections.
8. ZINSSER, HANS: Textbook of bacteriology, 5th edition, 1925.
9. GOODMAN, LOUIS and GILMAN, ALFRED: The pharmacological basis of therapeutics, 1941, Macmillan Company, New York.

# MENINGOCOCCEMIA WITHOUT MENINGITIS; A STUDY MADE AT THE STATION HOSPITAL, FORT GEORGE G. MEADE, MARYLAND \*

By HAROLD W. POTTER, F.A.C.P., Lt. Col., MC, ORC, ROGER D. REID, Major, Sanitary Corps, ORC, and LEWIS H. BRONSTEIN, Capt. MC, AUS, *Fort George G. Meade, Maryland*

MANY contributions have appeared in American and foreign journals describing meningococcemia without meningitis. Most of the reports have been of one to three cases with a discussion of the literature. Because of the wide distribution of such reports, it is not our purpose to summarize these findings but to report our observations on 11 cases which we treated. Sulfadiazine was the drug used in our series and, because of this, we have observed certain differences from the cases seen previous to this form of therapy. The outstanding difference is that our cases would fall into the acute meningococcemia class rather than in the subacute or chronic group, which has been the classification used prior to this.

Excellent discussions of the syndrome, as recent as 1939, are available, and the study of these articles will be sufficient to give one a good idea of the condition as well as a pre-sulfonamide view of the vagaries of the disease. Binns and Fothergill<sup>1</sup> have an excellent review of the literature up to 1931 with a description of the syndrome and a report of one case. Carbonell and Campbell<sup>2</sup> describe three cases and present a description of the disease from a study of 33 cases which they collected from the American literature up to 1938. Applebaum<sup>3</sup> reports a summary of 15 cases of his own, seven of which subsequently developed meningitis. In 1939, Heinle reported five cases.

Since the inauguration of sulfonamide therapy, there have been several individual case reports. In the Australian literature, Moss<sup>4</sup> reports four cases treated with sulfapyridine as well as an excellent discussion of the disease. In the American literature, Watson<sup>5</sup> reported one case treated with sulfanilamide and he also reviews the literature. He states that 12 cases had been reported since the start of sulfonamide therapy without a fatality. Kattwinkel<sup>7</sup> also reported one case treated with sulfanilamide.

The following is the abstract of our case histories in chronological order:

*Case 1.* G. G. was admitted to the Station Hospital on December 24, 1942, complaining of chill, generalized malaise, aggravation of the symptoms of an upper respiratory tract infection which he had had for the previous two weeks, severe headache and a rash. All the above occurred within 24 to 36 hours of the time he was admitted to the hospital.

Examination revealed that he did not look more ill than other patients with an upper respiratory tract infection. There was a generalized fine petechial eruption

\* Received for publication November 11, 1943.

that was prominent on the extremities. Some lesions were also present on the buccal mucosa but none was seen on the palate. There was no nuchal rigidity, but some pain was present at the base of the neck on extreme flexion and rotation.

His white blood cell count was 28,400 with 31 young and 63 segmented granulocytes. The spinal fluid contained three white cells of which two were granulocytes and one was a lymphocyte.

He was placed on the usual sulfonamide therapy. That afternoon, he complained of pain in both knees and elbows; the right elbow had ten degrees limitation in extension. By December 27, the eruption had almost entirely disappeared but the joint pain and involvement had progressed. At this time his left wrist, metacarpophalangeal joint of the left index finger, right elbow, right wrist, and left knee were definitely swollen and tender. No heart murmurs were heard. The liver and spleen

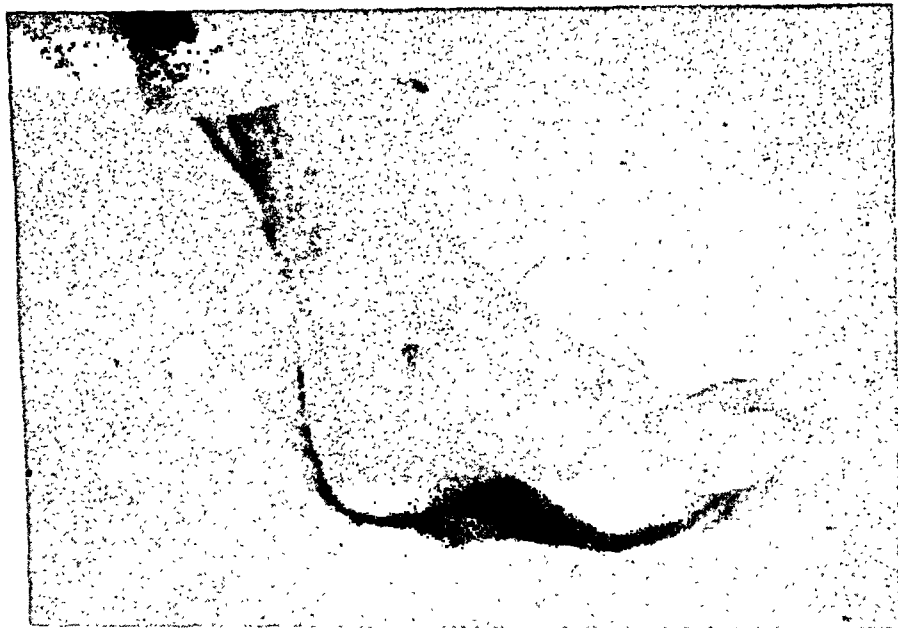


FIG. 1. Bullous lesions on foot in case of meningococcemia.

were not palpable. A platelet count on December 26 was 152,000. The white cells were 14,350 with 2 young and 79 mature granulocytes. The sulfadiazine was discontinued on the assumption that this patient had rheumatic fever and salicylates were administered.

On December 28, the left knee was normal, but the other joints were still involved. At noon, it was reported that a Group I meningococcus was found in the blood stream and sulfadiazine administration was resumed.

On December 30, the petechial eruption was entirely gone. By that date, all the joints except the right elbow had returned to normal. This joint continued to be swollen though less tender and red. Its motion was still limited. The orthopedic consultant saw him on January 5, 1943 and advised against tapping the joint at that time. The joint gradually became normal in size and by January 11, no abnormality could be made out. With active motion and physiotherapy, the pain and limitation of motion disappeared by February 22. A roentgenogram of the joint was taken on January 14 and showed some roughening of the trochlear notch which had the appearance of an old injury or osteochondritis.



Two electrocardiograms, taken on January 8 and January 28, were normal. The white blood cell count and differential count returned to normal on December 30, the seventh hospital day. The blood sulfadiazine level reached 14.1 mg. per cent at the height of therapy. The temperature reached a normal level on the sixth hospital day.

*Case 2.* V. E. J. was admitted on February 26 with a history of having felt perfectly well until the night of February 25 when he developed a chill while watching a moving picture. He felt feverish that night but went to his barracks to sleep. He awakened on February 26 with a persistent headache and slight cough. In the Receiving Office of the hospital, a rash was noticed.

Examination showed him to appear mildly ill. On his trunk and extremities, he had pink, dark red, and brown macules of various sizes. His throat was slightly injected. He had some muscle guarding of the neck but no rigidity. He had a questionable bilateral Kernig sign. His temperature was 101.8° F. and rose to 103.6° F. several hours later. Shortly before the rise in temperature he vomited twice. A spinal tap was done shortly after admission. The fluid showed five white cells, two of which were polymorphonuclears. The spinal fluid sugar was 71 mg. per cent and a trace of globulin was present. No organisms were grown on culture. The white blood cell count on admission was 26,000 with 80 per cent polymorphonuclears of which 20 were young forms.

He was seen by the Dermatologic Consultant on February 27, who described the lesions as pink macules with deeper colored centers and suggested that they were of the erythema multiforme variety.

On February 27, a Group I meningococcus was grown from the blood and the patient was placed on sulfadiazine. On February 28, the rash was fading rapidly but those lesions that were still present did not completely fade on pressure.

From this point on, he made an uneventful recovery. His temperature reached a normal level on February 28. The white blood cell count taken on March 1 was 7,500 with 45 per cent polymorphonuclears. The blood sulfadiazine level was 9.2 mg. per cent on February 28.

*Case 3.* M. G. L. was admitted on March 25, 1943 in a critically ill condition. He was in a state of mental confusion so that a complete history could not be obtained until three days later. The only complaint that could be elicited on admission was that of severe headache. Subsequently, he said that he had gone to bed the evening of March 24 feeling perfectly well. At midnight he was awakened with a severe chill and then developed fever. In the morning, he felt very dizzy, became extremely weak, and developed a headache which became progressively worse.

Examination was completely negative except for a marked purpuric eruption over his back, upper chest, and all extremities. His blood pressure was 60 mm. of Hg systolic and 40 mm. diastolic and his temperature was 103° F. A white blood cell count was 11,150 with 93 per cent polymorphonuclears of which 2 were myelocytes, 22 were juveniles and 30 were "stab" forms. The spinal fluid showed 2 lymphocytes, a sugar level of 77 mg. per cent and no increase in globulin. Culture of the fluid was negative. A Group I meningococcus was grown from the blood on March 26.

This patient was recognized as representing an early stage of the Waterhouse-Friderichsen syndrome. He was treated vigorously with sulfadiazine, intravenous glucose in saline, intravenous plasma, intravenous adrenal cortical extract, and intramuscular desoxycorticosterone. Full details of this case will be reported in a separate communication.

His temperature gradually dropped until it reached normal levels on his seventh hospital day. The rash completely disappeared by the sixth hospital day. The blood pressure gradually rose until it reached 100 mm. systolic by the seventh hospital day and a diastolic of over 60 mm. by the thirteenth hospital day. The white blood cell count came to normal levels on March 31 with 6,600 and 74 per cent polymorphonu-

ears. His blood sulfadiazine level was 17.5 mg. per cent on March 26 and 18.8 mg. per cent on March 27.



FIG. 2. Purpuric eruption on the legs.

He made an uneventful recovery after the first week of his illness although he did develop a bilateral muco-purulent conjunctivitis on March 30, which cleared in several days.

Case 4. W. A. M. was admitted the night of April 14, complaining of chills and headache. While he was on furlough on April 7, he had a severe chill, followed

by a short bout of fever and slight headache. The next day he felt weak, but he saw a physician who told him he had malaria, although no blood studies were done. At about the same hour on April 9, 11, 13 and 14, he had similar bouts of chills and fever. He had taken one quinine capsule a day since April 9. In addition to these recurrent bouts of chills and fever, he had a painful right elbow on April 11 and on April 14, painful swellings of the right and left ankle.

On admission, he appeared slightly ill with a swollen ankle. He had a scattered macular rash, resembling rose spots, over his chest and extremities. His temperature was 101.6° F. with concurrent pulse and respirations. A blood culture was taken and a spinal tap was done. The spinal fluid showed 6 lymphocytes. No organisms were grown from it. Blood smears for malaria showed no organisms. The white blood cell count was 12,150 with 92 per cent polymorphonuclears, 8 of which were young forms.

Because the possibility that this might be another case of meningococcemia was recognized, he was placed on sulfadiazine although rheumatic fever and malaria were considered as possible diagnoses. On April 16, he had a blood sulfadiazine level of 10.0 mg. per cent.

After the chill the night of admission, he no longer had either chills or fever. By April 18, the rash had completely disappeared and the joints were completely normal. On April 21, the eighth day after admission, the blood culture showed a Group I meningococcus.

The remainder of the course was uneventful. The white blood count of April 17 showed 3,900 cells with 66 per cent polymorphonuclears.

*Case 5.* A. W. F. was admitted to the Station Hospital on April 29, 1943 because of pain in his knees. This was of 16 years' duration, and apparently followed an automobile accident in 1927. General physical examination was negative and a roentgenogram showed early osteoarthritis with an osteochondroma of the right knee.

On May 11, while awaiting discharge from the Army, he had a chill followed by a recorded temperature rise to 100.4° F. At this time a generalized reddish, maculopapular eruption with a violaceous background was seen. A spinal tap was done and a clear fluid with three lymphocytes was obtained. A blood culture was taken. The blood count which had shown 9,200 white cells with 66 per cent polymorphonuclear cells now showed 10,200 white cells with 74 per cent polymorphonuclears.

The next day more lesions were seen. The dermatologist stated "if this patient appeared in the clinic, we would probably call this insect bites or some other type of bite, but since he is a hospital patient, will have to put this in the erythema multiforme group." New groups of lesions kept appearing and in some instances the older lesions developed hemorrhagic centers. The muscles were tender.

The first blood culture was reported as showing no growth but, because of the persistence of a low grade fever and new skin lesions, a second one was done on May 17. This condition continued until May 27 when, after five days of incubation of a third culture taken on May 23, a Group I meningococcus was discovered.

During the 16 days he was observed, the initial diagnosis of meningococcus septicemia was abandoned and diagnoses such as periarteritis nodosa and subacute bacterial endocarditis were considered. Biopsy of one of the skin lesions for a possible periarteritis nodosa merely shows a non-specific dermatitis with scattered collections of round cells, some polymorphonuclears, and plasma cells without definite relations to the skin appendages or arterioles. Some hemorrhagic areas were present.

Although he had no fever the day the blood culture was reported as positive, he was placed on the usual course of sulfadiazine. The blood count on May 28 was normal, showing 8,100 white cells with 57 per cent polymorphonuclears. The sulfadiazine level was 8.7 mg. per cent on this day.

Recovery was uneventful.

Case 6. L. J. E. was admitted to the Station Hospital on May 11 because of nausea and vomiting. He had felt well until 6 p.m. of May 10 when he became nauseated and vomited his dinner. He had several more vomiting spells with residual upper abdominal soreness but he had no diarrhea. He had a moderately severe headache.

He looked acutely ill with a temperature of 99° F. but no pathological findings were found on physical examination. His admission diagnosis was acute gastritis.

That afternoon his temperature rose to 103° F. but his headache had disappeared. Slight nuchal rigidity was present and a few spots, like rose spots, were seen on his abdomen. A blood culture was taken. A spinal tap revealed a clear fluid with one lymphocyte, a sugar level of 84 mg. per cent, and a trace of globulin. The white blood cell count was 10,990 with 82 per cent polymorphonuclears.

The next day, May 12, his second in the hospital, he developed pain and slight limitation of motion in the phalangeal joints of his right middle three fingers. On the following day these joints became swollen, red, and tender. The skin lesions had not changed and no new ones had developed. Because of the joint findings, he was placed on salicylates. Two hours later, the laboratory reported that a gram negative diplococcus, which later proved to be Group I meningococcus, had grown in the blood culture. He was started on intravenous sodium sulfadiazine, 5 grams.

The joints began to clear the next day so that by May 15, only the right ring finger was still swollen. This finger improved slowly so that it was May 25 before it had complete motion.

The white blood cell count became normal on May 17 with 5,500 cells and 59 per cent polymorphonuclears. The sulfadiazine level was 12.5 mg. per cent on May 13. The temperature became normal on his eighth hospital day.

Case 7. J. C. M. was admitted on May 13, complaining of a severe frontal headache that was noticed that morning. For the preceding week he had felt tired. The night preceding admission, he felt chilly but had no true chill. He awoke the morning of admission feeling quite drowsy and with a severe headache.

On examination he had a few violaceous reddish macules, which disappeared on pressure on his upper chest and abdomen. Otherwise no pathological findings were noted. He did not appear ill.

His temperature was 100° F. with corresponding pulse and respiratory rates. A spinal tap showed 7 cells with 1 polymorphonuclear and 6 lymphocytes. The sugar was 66 mg. per cent and the Pandy was negative. A blood culture was taken. Sulfadiazine therapy was started because it seemed that this was another case of meningococcemia.

On May 15, a Group II alpha meningococcus was grown from the blood. The rash was completely gone by May 16. The blood sulfadiazine level taken on May 14 was 17.5 mg. per cent. The temperature became normal the day after admission and remained so until discharge from the hospital.

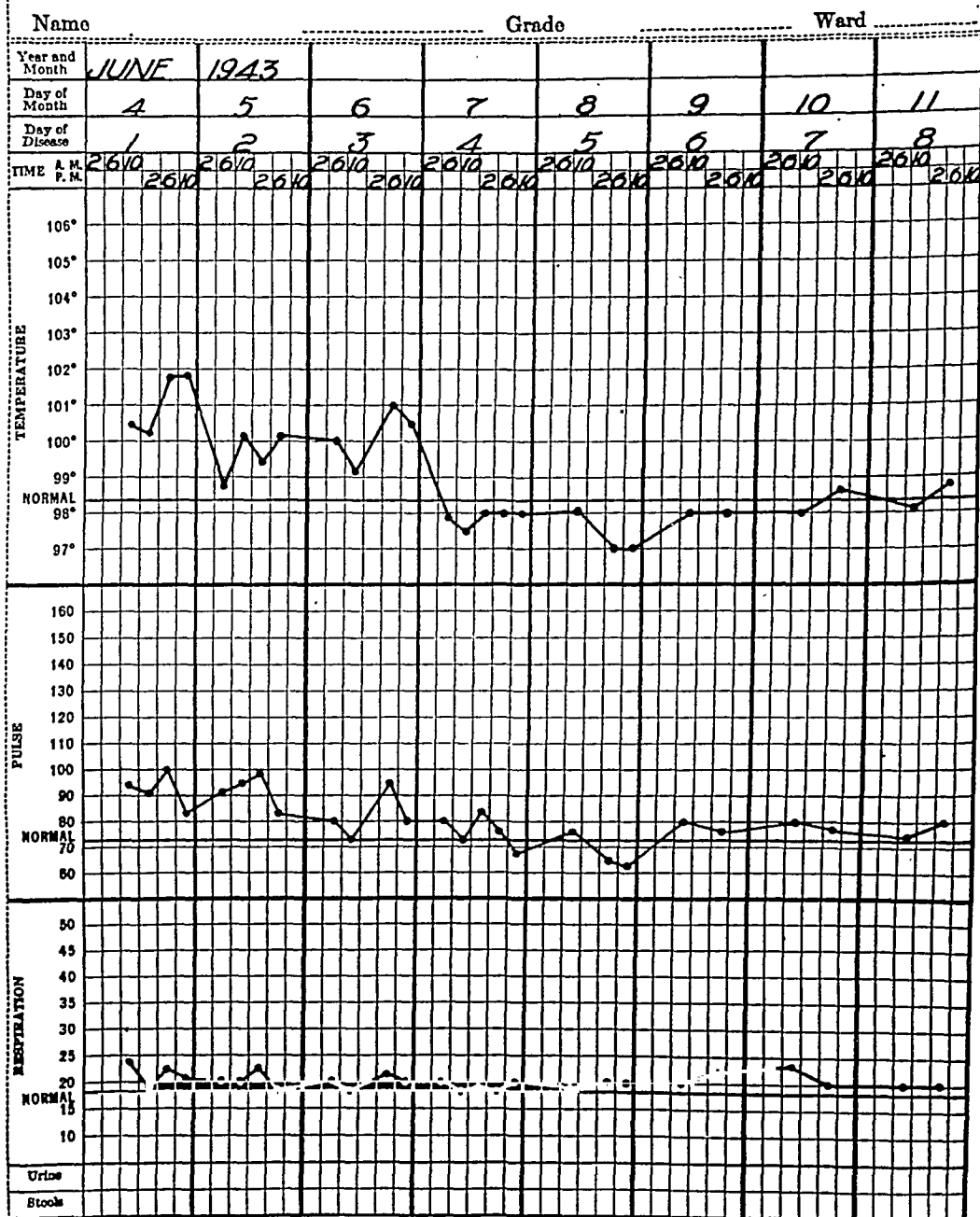
His entire course was uneventful.

Case 8. W. C. W. was admitted on June 1, complaining of cough and aching in both legs. He had been discharged from the hospital several days before, after having apparently recovered from an upper respiratory infection. He developed his muscular and substernal aches the day before admission. His nose was obstructed and he had a slight headache.

Examination showed only a congested nose and injected throat. His white blood count was 10,200 with 58 per cent polymorphonuclears. He ran an irregular course of fever with red, slightly tender, elevated spots on his chest and feet. On June 12, all the skin lesions had disappeared, the temperature was normal, and he felt well. On June 15, his temperature rose slightly, joint pains inconvenienced him, and several new skin lesions, this time looking like mosquito-bites, developed.

Form 55 H-2  
MEDICAL DEPARTMENT, U. S. ARMY  
(Revised May 31, 1939)

# TEMPERATURE GRAPHIC CHART



\* USUAL TYPE

16-17084

FIG. 3. Temperature chart from case of meningococemia showing curve of usual type.

Form 65 H-2  
MEDICAL DEPARTMENT, U. S. ARMY  
(Revised May 21, 1922)

TEMPERATURE GRAPHIC CHART

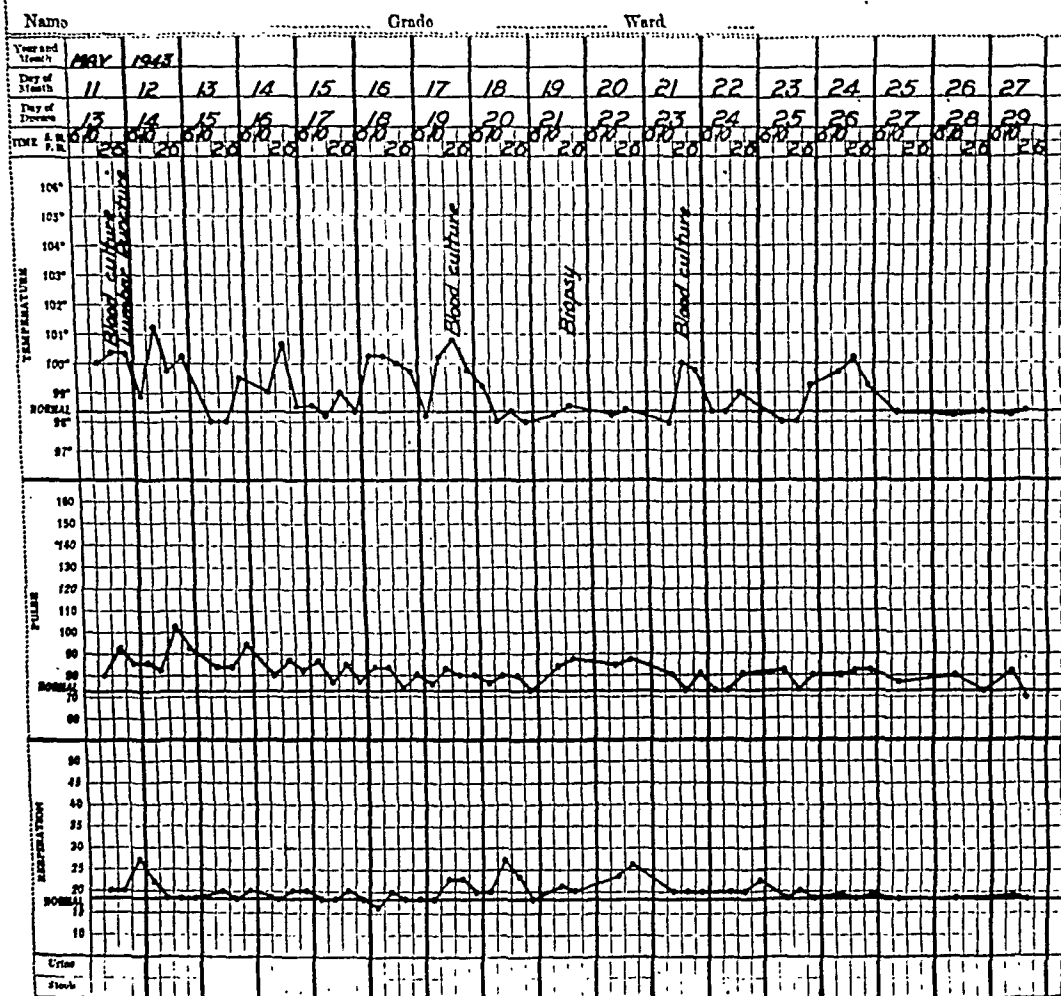


FIG. 4. Temperature curve of intermittent type.

On June 17, his temperature rose suddenly to 104.2° F. and a new painful lesion was seen on his left forearm. Physical examination otherwise still revealed no pathological findings but blood for culture was taken. The white blood cell count was 10,900 with 77 per cent polymorphonuclears of which four were young forms. The following day a Group I meningococcus was isolated from the blood. The rash became more widespread and now looked like those seen in previous cases of meningococcemia, round, pinkish macules with a violaceous background. A spinal tap showed 4 lymphocytes in the fluid which was sterile on culture.

Although the temperature had returned to normal by the time the blood culture report was received, he was placed on a course of sulfadiazine. The blood sulfadiazine concentration, 24 hours after starting therapy, was 10.8 mg. per cent. The white blood count on June 21 was 9,750 with 52 per cent polymorphonuclears. The rash completely disappeared by June 19 and his further course was uneventful.

*Case 9.* C. P. was admitted to the hospital on June 4, 1943, complaining of a frontal headache, aching in his muscles, bones, right ankle, both hips and both shoulders. His illness had started the afternoon of June 3 after he had returned from a 10 day leave. He took 40 grains of aspirin within six hours of the onset of his illness without any relief of the headache. The night of June 3 and 4, he had a severe chill. When he awakened on June 4, he noticed a rash.

Physical examination showed him to appear moderately ill with a temperature of 100.5° F. and corresponding pulse and respirations. His throat was injected. The neck was not rigid and a questionable bilateral Kernig sign was present. He had varied sized macules over his trunk, anteriorly and posteriorly, and all over his extremities.

The white blood count was 19,950 with 85 per cent polymorphonuclears, 12 of which were young forms. The spinal fluid was clear with three cells, two of which were polymorphonuclears. The spinal fluid sugar was 81 mg. per cent and no globulin was present. No growth was obtained on culture.

A blood culture was taken and the patient was placed on a course of sulfadiazine because it was assumed that he had a meningococcemia, although the ward surgeon stated, "eliminate erythema multiforme." On June 7, the blood culture had yielded a Group I meningococcus organism. On June 5, the day after medication was begun, the rash began to fade. It had completely disappeared by June 7. He had a blood sulfadiazine level of 9.6 mg. per cent 24 hours after the start of therapy. His temperature became normal on June 7 and he made an uneventful recovery.

*Case 10.* G. J. K. was admitted to the hospital on June 15, 1943 with a history of having had coryza for the two preceding days. The morning of admission his coryza had become worse and he developed a mild chill, malaise, sore throat, a slight cough and some frontal headache.

On examination he appeared slightly toxic with a temperature of 103° F. The only pathological physical finding was a congested nasal and pharyngeal mucosa. The white blood cell count, taken on June 16 was 15,450 with 81 per cent polymorphonuclears, 3 of which were young forms.

The day of admission he vomited once and then seemed to improve. His temperature reached 99° on June 17 and he felt well. On June 18, his temperature began to rise and he felt quite ill. His headache recurred and he developed a widely scattered maculo-papular rash on his trunk and extremities resembling mosquito-bites. Several hours later, some of the lesions formed hemorrhagic centers. The ward surgeon suspected meningococcemia and transferred him to the isolation ward. Sulfadiazine was started after spinal tap and blood cultures were done.

The spinal fluid showed 18 cells, 5 of which were polymorphonuclears and 13 lymphocytes. Culture resulted in no growth of organisms. A white blood cell count was 11,050; no differential count was done. The blood culture yielded a Group I meningococcus on June 21. The blood sulfadiazine level on June 20 was 12.0 mg. per cent.

The macules developed the typical violaceous background the next day, by which time the temperature had dropped to normal. It remained so for the rest of his hospitalization. The white blood count was normal on June 21. By June 22, the rash had completely faded and the remainder of his stay was completely uneventful.

*Case 11.* W. C. was admitted on June 30, 1943, complaining of pain in his chest, chills and fever, nausea and vomiting, and headache. He had had an upper respiratory infection for the week prior to his admission, with some nausea and occasional vomiting for the month preceding this. During the night he was awakened by a chill and pain across both sides of the upper part of his chest. He subsequently developed a severe headache.

His temperature was 102.2° F. and shortly after admission rose to 104°. Examination showed some impaired resonance over the left upper chest as the only pathological finding. Because the entire picture seemed to be one of pneumonia, a blood culture, sputum examination, and portable roentgenogram of the chest were done. The white blood cell count was 27,250 with 90 per cent polymorphonuclears of which 17 were young forms. The sputum did not contain sufficient pneumococci for typing. The roentgenogram was poor because of respiratory motion but a suggestive shadow extending from the right hilus towards the apex of the lungs was noted.

The next day the temperature came down to normal and the patient felt well. Subsequent roentgenogram showed the lung fields to be clear. On July 3, a Group I meningococcus had been isolated from the blood culture. Despite his apparent well-being and lack of any pathological physical findings, he was placed on a course of sulfadiazine. His blood sulfadiazine concentration after 24 hours was 7.3 mg. per cent. The white blood cell count on July 5 was 5,650 with 52 per cent polymorphonuclears.

He ran an uneventful course.

Most of the cases reported in the literature discuss the syndrome from its standpoint of chronicity, i.e. the length of time symptoms were present before the patient presented himself for study or before diagnosis was made. In all of our presented cases, symptoms were not present longer than two weeks before the diagnosis was made. Some of the cases had symptoms of upper respiratory infection for a short time before the acute onset. Case 1 had an upper respiratory infection for two weeks. Case 4 had chills and fever for one week before we saw him, and he was diagnosed as malaria elsewhere. This diagnosis has been made in previously reported cases. Case 5 developed his symptoms while in the hospital for another disease. His course, before the diagnosis was made, also simulated malaria. However, because the patient was seen throughout his course, other diagnoses such as subacute bacterial endocarditis and peri-arteritis nodosa were made in addition to meningococcemia. Case 6 had vague symptoms for a week prior to his acute onset. Case 7 had been in the hospital for an upper respiratory infection and had only been discharged a few days prior to his readmission. He ran a very irregular course for 16 days before acute symptoms suggested the possibility of meningococcemia. The symptoms in the other six cases began within several days of their admission to the hospital and the beginning of therapy.

The outstanding finding and the one which we have found most useful in calling our attention to the diagnosis is the skin eruption. Practically all the reported cases note the presence of some eruption. In only one case, number 11, was the rash absent. This case was also the most atypical in that it seemed to be a case of pneumonia on admission, and only because a routine blood culture was taken, was the organism found. In two cases, 1 and 3, the eruption was petechial and purpuric. Case 3 was a severely ill patient. The other eight cases presented variations of what we and others consider to be the basic type of eruption such as was seen in cases 7 and 9. This eruption is a round or oval macule or maculo-papule, pinkish in color and



with a violaceous background. It is generally on the extremities. We have never seen it on the face. It has more of a rose spot appearance because the violaceous hue was missing. When the individual becomes hemorrhagic center, it tends to look like the beginning of erythema multiforme. This was best seen in case 10. Instead of a purpuric center, this portion was raised, giving the lesion the appearance of a mosquito bite. When it appears, a hemorrhagic area takes its place and the lesion becomes multiforme. Cases 5, 8, and 10 illustrate this feature. In case 8, did the lesion have any resemblance to the British case reports suggest that they have seen a tender nodule. Our case, however, subsequent lesions which were more typical.

The rash usually had begun to disappear by the time the drug and clears entirely in several days. The individual becomes brownish, smaller, and then disappears. When the branny desquamation is seen. In those cases where fever rises, i.e. the malarial type, the lesions fade and reappear with each rise in fever.

The rash was also seen in a fair proportion of cases to develop meningococcus meningitis. A survey of 100 cases of meningitis in which the organism was grown from the blood and both revealed six cases which had a rash like that seen. However, in only one of these six cases was the blood culture positive. In the other five, the organism was grown only from the cerebrospinal fluid. Unfortunately we did not attempt to puncture the skin lesions. The meningococci were present in the macules. The organism on a skin lesion merely showed a non-specific culture. Cultures were not done because the search was for lesions of peri-arteritis nodosa. Thus we cannot state whether the skin lesions are responsible for the lesions.

Joint and muscle pains form another outstanding feature of the syndrome. The various authors who have reported this fact. In many instances it has been responsible for the diagnosis of malarial fever as occurred in our case 1.

In our 11 cases, five had no signs or symptoms of joint and muscles. In three of the remaining six, there were complaints of joint and muscles. In case 5, there were not only muscle pains but the muscles were quite tender to touch. It was this feature of the syndrome which suggested the diagnosis of peri-arteritis nodosa. In the three cases, there was swelling, redness, and limitation of movement.

cleared rather quickly under sulfadiazine therapy. In no case, was there any residual loss of function.

None of these joints was tapped. One of our meningitis cases did have a knee joint tapped after several days of sulfadiazine therapy. The fluid was purulent, no meningococci were cultured, and the sulfadiazine concentration in it was almost as high as the blood sulfadiazine level.

Schein<sup>8</sup> discussed this complication of meningococcemia in the pre-sulfonamide days. He reported three cases in which destruction of the involved joint occurred, but the general consensus is that such an outcome is unusual. It may very well be that such involvement may not occur when sulfonamides are used, particularly if the disease is recognized early, because recovery is rather rapid.

There were no outstanding neurological findings. Headache was the most frequent complaint. In seven of the cases it was severe enough to be a major symptom. In three it was slight and could have been part of the malaise that these patients experienced. One patient did not mention this symptom. In only one case, number 5, was slight rigidity of the neck noted. In two of the cases a questionable Kernig sign, which usually means a negative one, was elicited.

In 10 of the cases a spinal tap was done. No organisms were seen on direct smear nor were any organisms found on culture. There are no definite criteria for the cellular content of a normal spinal fluid. Todd and Sanford<sup>9</sup> state that 10 cells are usually accepted as the maximum number in health with nearly all being lymphocytes. On this basis, seven of our cases definitely fall into normal limits. Case 2 had five cells, two of which were granulocytes. This patient had a severe headache and a questionable Kernig sign. Case 9 had three cells, two of which were granulocytes. He had the same findings. These patients had short illnesses prior to the spinal tap and might have gone on to meningeal involvement with less intensive therapy. However, the sugar and globulin content in both of these fluids were normal. This, together with the fact that the further clinical course did not result in meningitis and that no meningococci were grown from the fluid on culture, leads us to include them as cases of meningococcemia without meningitis.

Case 10 had the greatest number of cells, 18, but only five were granulocytes. This patient, however, had only a slight headache and no neurological signs. Several days elapsed between the onset of symptoms and the performance of the spinal tap. The predominance of lymphocytes among the 18 cells, the absence of severe headache or neurological signs, also permits us to include this as a case of meningococcus septicemia without meningeal involvement. We have no explanation for the increased cell count other than the possibility of slight trauma while performing the tap and the counting of red cells as lymphocytes.

We have not experienced the difficulty reported by others in isolating the meningococcus. In one case, number 4, it took eight days before the

blood culture was reported as positive. In case 5, it took three blood cultures and a five day incubation of the third to isolate the meningococcus. In the other nine cases positive reports were returned in several days. We have not had to enrich the medium as has been suggested by practically all the other authors by adding ascitic fluid or other agents.

The technic for culturing the blood and spinal fluid has been as follows: The media used are: (1) pork infusion broth, (2) thioglycollate medium, Brewer,<sup>10</sup> (3) pork infusion agar and (4) chocolate agar. The infusion and broth and agar are prepared as described in Technical Manual, 8-227, War Department<sup>11</sup> using pork instead of beef or veal. (1) and (2) are inoculated at the bedside with 10.0 c.c. and 1.0 c.c. of uncitrated blood while blood agar plates are made by adding 1.0 c.c. of the citrated specimen to 10.0 c.c. of pork infusion agar in the laboratory. Cultures are incubated at 36° C. aerobically except for one blood agar plate which is placed in a Brewer anaerobic jar.

Sediment from centrifuged specimens of spinal fluid is inoculated with drops from a capillary pipette with a platinum loop into chocolate agar plates prepared from Dextrose Proteose No. 3 agar plus heated blood<sup>12</sup> and into thioglycollate medium.

All of the above media can be obtained in dehydrated form from supply houses or can be made from chemicals, ground meat and peptones, readily available. Heated blood used in making "chocolate" agar is the only enrichment material used.

That the above technic is adequate is evidenced by the fact that in only four cases of clinical meningococcus infection, with and without meningitis, out of more than 70 cases have we failed to isolate the organism.

Other laboratory findings were not characteristic.

All of our cases were treated with sulfadiazine. If the patient could not tolerate the medication by mouth, he was given 5 grams of sodium sulfadiazine intravenously followed by 1 gram every four hours, the route depending upon the patient's condition. If he could take the drug orally, the initial dose was four or six grams depending on his apparent condition. Fluids were given, as indicated, to assure a urinary output of 2,000 c.c. in 24 hours. Blood and urine examinations were done routinely to anticipate toxic reactions, but none was seen in our cases. The medication was continued, as a rule, for six to eight days and, in any case, until the temperature remained within normal limits for several days.

Our cases presented a wide variety of types. A malaria-like course was seen in two. Predominant joint involvement suggesting rheumatic fever was also present. One patient resembled a case of severe gastritis. Others presented varying pictures. Our last case had the clinical appearance of pneumonia and was recognized only because of a routine blood culture. Awareness of the possibility of the infection and the appreciation of the nature of the rash were the most important factors that enabled us to make

the diagnosis. The headache, though frequent, is too common a complaint to have a great deal of significance alone, but with the other findings, it is important.

### SUMMARY

1. Eleven cases of meningococcemia without meningitis are presented.
2. The diagnosis can be strongly suspected before the report of the blood culture in a patient with the skin eruption and headache if the possibility of this disease is kept in mind.
3. Sulfadiazine resulted in rapid cure without sequelae in all our cases.

### ADDENDUM

Since the above article was written, we have seen four additional cases of meningococcemia. In general, they tended to fall into the groups described above. One case had a temperature curve that was intermittent in type, whereas the other three had the usual course of fever for several days with a more or less sudden decline to normal after sulfadiazine was started. One case developed a rigid neck about 12 hours after the drug was started, but a spinal tap was not done. It was felt he had probably developed meningitis. His rash was entirely purpuric, and meningococci were demonstrated on examination of the tissue juice from his skin lesions.

Another patient had the macular type of lesions, some of which developed purpuric centers. Two of these on the foot became quite large and were ultimately seen as large bullous lesions. These are shown in figure 1.

The third had only macular lesions, from which meningococci could not be demonstrated in the tissue juice. The fourth had both purpuric and macular lesions but the latter predominated.

Figure 2 shows the distribution of the purpuric lesions as they appear on the extremities and, of course, give the name of spotted fever to the disease. It is lesions such as these that may make one consider typhus or Rocky Mountain spotted fever as a possible diagnosis.

All the cases recovered.

The attempt to demonstrate the organisms in the lesions is in agreement with the report made by Tompkins,<sup>1a</sup> who demonstrated the organism in skin lesions of the purpuric variety but not in the macular variety. It may be that the macular lesions are a manifestation of toxin production, whereas the purpuric are due to destruction of the capillary wall by the organisms themselves. The macular lesions that develop purpuric centers may be due to a more intense action of the toxin or to the action of the organism after the toxin has acted. We hope to do more studies in future cases on the demonstration of organisms in the various skin lesions in these cases.

In three of the cases the first blood culture became positive in 24 to 48 hours. In the fourth case, a second blood culture had to be taken and was positive after 24 hours of incubation.

### BIBLIOGRAPHY

1. BINNS, J. F., and FOTHERGILL, L. D.: Chronic meningococcic septicemia, *New England Jr. Med.*, 1931, ccv, 536-539.
2. CARBONELL, A., and CAMPBELL, E. P.: Prolonged meningococcemia: report of three cases, *Arch. Int. Med.*, 1938, lxi, 646-654.
3. APPLEBAUM, E.: Chronic meningococcus septicemia, *Am. Jr. Med. Sci.*, 1937, cxci, 96-108.
4. HEINLE, R. W.: Meningococcic septicemia: report of five new cases, *Arch. Int. Med.*, 1939, lxiii, 575-583.
5. MOSS, G. C.: Meningococcal infection with special reference to meningococcal septicemia, *Med. Jr. Australia*, 1941, i, 548-552.
6. WATSON, L. D.: Meningococcemia without meningitis, case, *New England Jr. Med.*, 1941, ccxxv, 685-686.

7. KATTWINKEL, E. E.: Meningococcemia, *New England Jr. Med.*, 1941, ccxxiv, 685-686.
8. SCHEIN, A. T.: Articular manifestations of meningococcus infection, *Arch. Int. Med.*, 1938, lxii, 963-978.
9. TODD, J. C., and SANFORD, A. H.: Clinical diagnosis by laboratory methods, 1942, Ninth Edition, W. B. Saunders Co., Philadelphia, Pa.
10. BREWER, J. H.: Clear liquid medium for "aerobic" cultivation of anaerobes, *Jr. Am. Med. Assoc.*, 1940, cxv, 598.
11. Technical Manual 8-227: Methods for laboratory technician, War Dept., October 17, 1941, page 157.
12. REID, R. D.: Isolation and identification of the gonococcus, *Bull. Johns Hopkins Hosp.*, 1942, lxx, 370.
13. TOMPKINS, V. N.: The diagnostic value of smears from purpuric lesions of the skin in meningococcic disease, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 31-32.

## MEDICAL PROBLEMS IN THE MIDDLE EAST\*

By CRAWFORD F. SAMS, Colonel, MC, *Carlisle, Pennsylvania*

THE medical problems in the Middle East Theatre of Operations which I will mention and discuss have either been published or mentioned on the radio; otherwise I could not discuss them. For the same reason of security, as it is called in the military service, it will not be possible to give specific rates concerning the incidence of these diseases among our troops.

I shall not include in this discussion anything about the fighting; or problems of evacuation of battle casualties, of which we had a considerable number in that theatre, as certain American units supported the Eighth Army in its advance across Africa from El Alamein to Tunis and into Sicily; but shall consider only problems pertaining to internal medicine.

As Surgeon of the United States Military North African Mission, and later as Chief Surgeon of the United States Army Forces in the Middle East, I was responsible for the organization and establishment of the medical service for all of our forces in the Middle East. There are now many American hospitals throughout the area from Tunisia through Tripoli, Benghazi, Cairo, the Levant, and on into Persia. Those were some of my hospitals.

In order to understand the distribution of the diseases encountered in this theatre, it will be necessary to consider the geography and climate because these factors affect disease. The Middle East is rather a large area. On an ordinary map, Africa and Europe are usually shown in order to include the countries in the Middle East; and, therefore, the countries look relatively small. The Middle East consists of Iran, Iraq, Turkey, Syria, Palestine, Transjordan, Saudi-Arabia, Egypt, Libya, Anglo-Egyptian Sudan, Eritrea and Ethiopia. The entire Middle East is much larger than the United States. The distance from an American hospital—for example in Persia—to one in Tunisia is over four thousand miles; much farther than it is from New York to San Francisco.

Many people think of Africa as a country of jungles. Actually, there is no jungle anywhere in the Middle East Theatre. The jungle in Africa is in West Central Africa. It does not extend into the Middle East or the North African Theatre areas. The countries of the Middle East vary, just as different parts of the United States vary from each other, as far as climate and the character of the country and the distribution of diseases are concerned. In the northern part of Persia, there are very high mountains, sixteen to eighteen thousand feet high. There is snow on these mountains even in the summer. On the other hand, in the southern and central parts of

\* Presented before the Sixth Annual Regional Meeting of the American College of Physicians in Philadelphia, November 19, 1943.

Persia, from the foot of the mountains down to the Persian Gulf, there is a desert with extremely high temperatures. Consequently, in different parts of Persia one may expect entirely different problems in health, and differences in the distribution of diseases. In the southern part of Persia, the so-called desert area, temperatures range from  $135^{\circ}$  to  $145^{\circ}$  in the summer. In Iraq, the Tigris and Euphrates Rivers join together to form the Shat-al-Arab. This country, particularly in the central and western portions, is desert. At the junction of the two rivers is the fabled site of the Garden of Eden, and a little farther to the west are the ruins of Babylon, which have been excavated. Evidence shows that at one time this part of the world was thickly populated and highly developed from an agricultural standpoint. Now it is only desert. There is also evidence to show that the depopulation occurred probably as a result of malaria.

Syria and Palestine farther to the west are entirely different from Iran and Iraq. There are mountain ranges parallel to the shore of the Mediterranean, and the country is highly developed and rich in agricultural land. The mountains are so high in Syria that skiing takes place as late as May. The climate along the Levant, as it is called, is almost ideal. In fact, it is quite similar to our California climate. Between the mountains and the sea, along the coastal plains, citrus fruit groves are found, particularly in Palestine. The coastal plain is rather thickly populated with many small villages and cities, including the beautiful city of Tel-Aviv on the coast of Palestine. In Palestine the modern buildings and relatively modern sanitation in the Jewish cities and towns which have been built within the last twenty years contrast with the mud hovels and total lack of sanitation among the Arabs and their villages.

Saudi-Arabia was of no particular concern to us. It is largely desert, sparsely inhabited, and the interior of the country is barred to Christians. Even aircraft travel over the central part, around Mecca, is forbidden lest it offend the Mohammedan people, who largely populate the Middle East. Egypt is entirely different from any other country in the Middle East. Although the chart shows it to be rather a large country, actually some fifteen million people are concentrated in a triangle about one hundred miles on each side. The triangle called the Delta is like a funnel and extends from Alexandria to Port Said and down to Cairo. There is a narrow belt of cultivated land along the Nile as it runs through Egypt. This belt which may range from a few hundred yards to three or four miles, is also thickly populated. The remainder of the country is largely made up of rocks, desert, and mountains which are entirely barren of all vegetation.

The Anglo-Egyptian Sudan is really a continuation of Egypt, as far as the character of the country is concerned. However, in the extreme southern parts there are marshes and swamp lands in which are found much large game. Eritrea and Ethiopia are very similar. They are very rugged countries with high mountains, again sixteen thousand to eighteen thousand

feet high. The country is primitive and so are the people. Considerable developmental work was done during colonization by the Italians who built some very beautiful cities and very fine roads. There is one spot in Eritrea, the seaport of Massaua, which is comparable in climate to Southern Persia. This port of Massaua has also a high humidity so that it is extremely difficult for Occidentals to live and work in that port continuously. The Italians had a rest camp up in the mountains about forty miles away to which they took their people several days each week.

Libya extends along the southern edge of the Mediterranean from the border of Egypt to Tunisia. Around Benghazi in what is called the Benghazi Hump, as far east as Derna, the country has been rather highly developed agriculturally by the Italians. The climate is pleasant. Tripoli, farther to the west, is a beautiful resort city, and the surrounding country for miles around has been highly developed. There are beautiful estates surrounding the city of Tripoli. Excluding the principal areas around Tripoli and Benghazi, the country is rocky and sandy, much like the country in Nevada and Utah. Although the temperatures were as high as  $120^{\circ}$  last summer in Tripoli, still the nights were cool and the climate on the whole is not unpleasant.

The eastern edge of Tunis as far north as the town of Enfidaville, a little way south of the city of Tunis, came within the boundaries of our theatre during the march to Tunis as the Middle East forces pushed up from the Mareth Line. The country along this eastern part of Tunis is not unlike some parts of Pennsylvania. There are wheat fields, orchards and many cattle. It is highly cultivated, and there are some very nice little cities. It was quite chilly in Tunis last May and June, and wool clothes were comfortable. This very brief and sketchy description of the various countries of the Middle East shows that it is far different from the country most of us ordinarily think of as constituting that part of the world. It is not terrifically hot all over the Middle East. Excessive heat occurs only in the two areas mentioned. There is no jungle and the desert is not just sand.

The environment, habits and ways of living of the people who inhabit this part of the world also determine the distribution of diseases with which we are concerned. All of this part of the world might be called the Arab world, as it is largely inhabited by Arabs. Most of these people are Mohammedans and therefore have certain customs which differ markedly from ours. The great majority of the adult natives throughout this part of the world are the survivors of many diseases. Owing to their habits, practically all of these people are exposed to typhoid fever, dysentery, malaria, sand-fly fever, small-pox and typhus. In one area the infant death rate as far as we were able to determine was eight hundred per thousand; in other words, eight out of ten babies died before they were a year old. In another area, three out of ten died before they were a year old, and half of the survivors died before they became adults. Most of them died, I think, of typhoid fever or dysentery.



Diseases of the intestinal tract, such as typhoid fever, bacillary dysentery and amebic dysentery are all prevalent throughout the entire middle east. The habits of the people are responsible for the almost universal infection of the population with these diseases which have such a high mortality among infants and little children. In fact, typhoid fever is considered a child's disease in the Middle East. As a result of the universal infection, the carrier rate among the survivors is exceptionally high.

These people do not use toilets and contaminate the ground along streams. A typical scene along any stream or canal will show individuals contaminating those banks or the stream itself with feces and urine. Then nearby there may be others washing their clothes and still others bathing. Then on down the stream there may be women dipping up the water which has been contaminated into large jars for drinking purposes or drinking out of their cupped hands directly from the stream or canal.

As another example, in one large city, relatively modern in as far as the buildings are concerned, the water supply is obtained from snows melting on the mountains. The water is brought down to the city in underground channels. However, when it reaches the city it is turned out into the gutters of the streets and there one may see people contaminating the water with human excrement, and bathing in the gutters, washing clothes and then drinking the water. In effect, these gutters are the combined water and sewage supply system of the city. Typhoid and dysentery, either bacillary or amebic, can be acquired only by taking into the intestinal tract in food or drink the organisms which have been excreted from the intestinal tract of others. The scenes just described illustrate one method of introducing these intestinal diseases into a large portion of the population.

However, another important method of dissemination in the Middle East is by the fly. Owing again to the contamination of the ground with fecal material, garbage, and refuse of all kinds as well, flies abound, and these flies which breed in this material contaminate their feet as they feed on the excrement of people who are carriers. Screening is practically unknown anywhere in the Middle East, and all the kitchens of the finest hotels are unscreened. The food becomes contaminated and you eat it and contract the disease.

A third method very common in the Middle East which also helps to spread the intestinal disease arises from the almost universal custom of irrigating gardens with sewage or highly contaminated water. It is unsafe to eat lettuce, radishes, raw celery, or any vegetable grown in the ground, or such things as strawberries, unless they can be cooked thoroughly in order to kill the bacteria which are on these vegetables as a result of the method under which they are grown. Amebic dysentery is most commonly transmitted by the eating of green vegetables which have been mechanically contaminated by human excrement either by direct fertilization or heavily contaminated water. For two years I did not have lettuce, radishes, or fresh strawberries or raw celery, and neither did I have dysentery.

In order to survive in the Middle East without contracting one of these intestinal diseases, it is absolutely necessary to follow certain simple rules, such as eating only thoroughly cooked food, or fruit which has to be peeled before it is eaten, by avoiding local ice cream or milk which has not been boiled. Americans are people with a great curiosity. When American troops first come to the Middle East and see a restaurant or a hotel which looks inviting, they'll go in and eat the things that are placed before them. As a result, immediately after every troop ship arrives, the sick rate for dysentery shows a sharp increase until that particular group of troops has been educated and discipline maintained in carrying out the very simple rules necessary to avoid dysentery or any of the intestinal diseases. We were able to demonstrate to the amazement of local health authorities that fly breeding could be restricted and that dysentery, typhoid and other intestinal diseases could be controlled at our bases in the Middle East.

Typhoid fever itself was not particularly a problem to our troops in the Middle East. All of our personnel are inoculated against typhoid, paratyphoid A and paratyphoid B, and this inoculation is most effective. However, dysentery was quite a problem, both bacillary and amebic. Where it was possible to make such surveys we found that the so-called "Gippy tummy," "Delhi tummy," "Teheran tummy" or "Massaua tummy" were all mild cases of dysentery, usually Sonne or Flexner in type. The onset is usually with diarrhea which may be accompanied by abdominal cramps. The stools run as high as twenty to thirty in 24 hours, and they may show blood and mucus macroscopically—almost all show blood microscopically. If untreated, the patient becomes dehydrated and rather toxic. These mild cases will usually subside in a week to ten days if untreated, but relapses are very frequent. Under the treatment which was in force in the Middle East in 1941, that is, giving a saline cathartic followed by paregoric and bismuth, these cases would usually respond in from four to five days. The more serious cases, showing blood and mucus, frequently had a prolonged and stormy course in hospital, and there is an appreciable death rate from bacillary dysentery. Many of the cases spent from a month to sometimes as long as six months in hospitals. Supportive treatment, such as intravenous fluid, was necessary. We were able to get a small quantity of sulfaguanidine which was used to treat the more serious cases, with dramatic results. Later, as larger quantities of sulfaguanidine became available, it was found that many of the milder cases of dysentery could be treated without hospitalization. Patients who had twenty to thirty stools a day, when treated with sulfaguanidine, in from twelve to twenty-four hours showed a diminution in the number of stools to perhaps three or four in twenty-four hours. The patients immediately became less toxic and often felt so well that they wanted to go back to duty. The very mild cases usually responded to treatment without hospitalization, simply spending a day in bed. The average quantity of sulfaguanidine required was one-quarter of a pound per patient for a large series of cases. Sulfaguanidine changed the entire picture of

the treatment of dysentery in the Middle East. Instead of being a disease which filled the hospital beds with patients for relatively long periods of time, with many of the patients seriously ill, our non-effective rate—that is, the number of patients in hospital constantly—was markedly reduced and the days spent in hospital were very few compared to previous experience. There were very few relapses among the dysentery cases treated with sulfaguanidine. Shortly before I left, sulfadiazine was being used also with excellent results in the treatment of bacillary dysentery.

A fairly large number of cases of amebic dysentery was found in routine stool examinations which were required of all patients entering hospitals for any cause. Many of these patients were absolutely symptom free or had only periodic attacks of mild diarrhea which were not severe enough to cause them to apply for medical attention. Amebic dysentery was particularly prevalent in Persia. The standard emetin treatment gave excellent results. Mixed infections of bacillary and amebic dysentery are more frequent than might be expected. Often the case coming in with severe diarrhea, prostration, blood and mucus when treated with sulfaguanidine would apparently clear up and then relapse after a few days. Stool examination showed amebae and treatment for amebic dysentery then was in order. *Entameba coli* was very common, and we had considerable difficulty initially in training laboratory technicians to differentiate between *Entameba coli* and *Entameba histolytica*. Initially, many cases of *Entameba histolytica* were reported which, when checked by well trained personnel, were shown to be *Entameba coli*. It was necessary to send a specially trained laboratory officer to all of our hospitals to give training to laboratory officers and technicians in this differentiation before the confusion between *Entameba coli* and *Entameba histolytica* could be cleared up. Of course many of our medical personnel in this country have had little experience in the identification of amebae in stools.

The hazard of malaria is by no means universal in the Middle East; in fact, the problem of malaria is fairly well localized. For instance, a highly malarious area exists in southern Persia along the Shat-al-Arab and Persian Gulf shore. It exists there primarily because that limited district is highly irrigated and full of date palms, as the packing and shipping of dates is the principal industry there. Places where mosquitoes breed abound, and the natives are infected. Most of the children acquire malaria either as babies or early in life after their first year and either die or recover from the clinical symptoms; that is, chills and fever. However, they still carry the plasmodia in their blood. Therefore, when troops enter an area, if the natives are allowed to come into our camps to work with our troops and live near our troops, if these natives are carriers of malaria; and if, at the same time, the species of *Anopheles* mosquitoes which can transmit malaria are present, then a high malaria rate among our troops can be expected. Malaria in the Middle East existed around the Persian Gulf and in Southern

Persia. It exists in the Jordan Valley in Palestine and up along the rivers of Syria and it exists along the Suez Canal and in the Egyptian Delta, and along the entire length of the Nile River. It exists in certain areas in Eritrea. It was said to occur around Benghazi and Tripoli and along eastern Tunis, but we found that it did not exist there. In only one place, a little town called Gabes, did we find malaria along the north coast of Africa east of Tunis. Malaria can be controlled under those conditions and we did control it. It is impossible to drain all the swamps or irrigated areas during a military operation. Neither is it economical to drain acres and acres of swamp when you may only be there a short time. The simplest and most satisfactory solution there was to train our troops in what we call malaria discipline—measures the individuals can take to protect themselves from the bites of an infected mosquito; such as repellents, the use of mosquito bars, and, where possible, screening of buildings. The simplest means was to keep the natives at least a mile or two away from our camps, because *Anopheles* mosquitoes may abound and still there will be no malaria unless there is some infected person within a mile or so who has previously been bitten by this *Anopheles* mosquito. An *Anopheles* mosquito ordinarily does not fly more than a mile. We did not use suppressive drugs in the Middle East theatre.

A number of cases of malaria acquired on the west central coast of Africa developed clinical symptoms after arriving in the Middle East. This malaria was malignant tertian. It might be well to emphasize the fact that malaria rivals syphilis as the great masquerader. It behooves all physicians in this country to become familiar with the symptomatology and the multitude of manifestations of malaria. Many of our men returning to this country are having, and will have, relapses. The importance of this is illustrated by two cases that occurred early in our experience. One case was a young man who had arrived in the Middle East from a highly malarious area about four days before his illness. He reported on sick call to a young doctor who also had recently arrived from the United States, actually from the northeastern part of the United States where malaria is not a problem. This patient complained of diarrhea and abdominal cramps with typical symptoms of "Gippy tummy" or a mild case of bacillary dysentery. This young doctor made the diagnosis of diarrhea, clinically. This patient was treated with magnesium sulphate, followed with paregoric and bismuth. There was no fever, no chills, no headache. The patient was marked "Quarters" and was put to bed. About eight hours later, this young physician was called by another soldier who stated that the patient had collapsed and was unconscious. The patient was immediately moved to the hospital; intravenous quinine therapy was started after a smear showed malignant tertian malaria. He died about two hours later. An autopsy showed the vessels in his brain filled with plasmodia.

The other case was also a young man who had arrived within less than a week and also complained of diarrhea and lassitude. He was seen by a

young medical officer who had had little experience with malaria. He was treated for his diarrhea with the usual saline purgative, followed by paregoric and bismuth. The man improved and was returned to duty. At no time did he have chills or fever or complain of a headache. The second night after being returned to duty, investigation showed that he got up to go to the latrine. He was found dead the next morning. Autopsy showed the usual picture of the cerebral type of malignant tertian malaria. It was necessary to issue instructions to examine a blood film for malaria in all men who had been in a highly malarious area who presented themselves on sick call or complained of headaches or abdominal symptoms. We made a survey of approximately one hundred men who had come across by air from west central Africa which is highly malarious, and found positive smears in 30 per cent of individuals without symptoms. All of these individuals were placed on a therapeutic course of treatment.

Another disease in the Middle East, called Pappatacci or Sand Fly Fever, is found throughout Persia. It exists in the Levant to a lesser extent. It is found in Egypt and in Libya. It was not a problem in Eritrea and Ethiopia. Like malaria, this disease is transmitted by an insect, in this case a sand fly. Before the sand fly can become infected, it must first bite an individual who is carrying the virus in his blood. If after a period of four to seven days, the sand fly bites another individual, it injects this virus into his blood stream. After a period of time he develops a terrific headache, fever and other symptoms of sand fly fever. A sand fly ordinarily doesn't fly more than 50 to 100 yards, and a person can be bitten by millions of sand flies and never get sand fly fever unless first they have had the opportunity of biting an individual who carries the virus in his blood.

The transmission of this disease is well illustrated by a small epidemic which occurred among our troops. In one locality it was convenient to place a battalion near the railroad yards, and barracks were built right across the street from a row of native mud and stone huts. These sand flies breed in piles of stone and mud—rubble it is called. Thus there were excellent breeding grounds for the sand fly right across the street. The natives furnished the reservoir of carriers because they carried in their blood the virus which causes sand fly fever. The sand flies that had become infected by biting the natives then flew across the street 50 or 75 feet, and bit our soldiers who sat around outside of the barracks in the evenings. Those barracks were screened; that is, the windows were screened with a wire netting called "sand fly screening," but in constructing the buildings they didn't put any screen doors on, only solid wooden doors and the soldiers in the hot weather naturally left the solid wooden doors open. That was a perfect setup for sand fly fever, and at the first outbreak an investigation was made as to the cause and it was perfectly obvious how it was being acquired. The necessary remedies were applied—and they were very simple ones indeed—and the epidemic was stopped. We found that oil sprayed on the ground

around buildings is an excellent repellent as far as sand flies are concerned. Screening of buildings—complete screening, including doors, that is—is also an excellent method of control. We do not have adequate knowledge about sand fly fever. It is known that carriers do exist in large numbers but how long an individual can remain a carrier after he has had the disease, is not known.

The diagnosis of sand fly fever is not satisfactory as it is made largely by the process of elimination. An individual who comes in with a severe headache, post orbital pain, general aching, high fever, who has no obvious localized infection such as a cold, tonsillitis, etc.—and who shows no malaria in blood smear, is diagnosed sand fly fever. I am not sure but that many mild influenza cases were confused with sand fly fever. A better method of diagnosing this disease was needed and a Neurotrophic Virus Disease Commission headed by Dr. Paul, of Yale University, is now in the Middle East, working on sand fly fever. They are attempting, first, to develop a diagnostic serological test for the disease; and second, to determine how long individuals may remain a carrier of the virus of sand fly fever. The textbooks we found were not accurate in some of the statements made about sand fly fever, particularly the duration of its possible carrier state. We were, of course, also interested in the method of controlling this disease. It is hoped that as a result of the work of this Commission our knowledge concerning sand fly fever will be increased.

Dengue is a disease which exists in the southern part of the United States. It was a problem in the Middle East only in one locality, around the harbor of Massaua. Dengue, like malaria, is transmitted by a mosquito, an *Aedes*. To become infected, the mosquito must first bite an individual who is carrying the virus in his blood. Owing to the fact that the particular area in which dengue existed was small, an insect control unit was put in the area and was able to control this particular type of mosquito. As a result of the work of the insect control unit, our troops did not become infected.

Typhus is another disease prevalent in the Middle East. It is a disease closely associated with war. During and after a war, people, particularly refugees, are crowded together. People come into communities where war work is being carried on and crowd together, particularly in cities. Under such overcrowding, people lack adequate bathing facilities and in the Middle East bathing is not too common anyway. Epidemic typhus is spread by lice which abound among these people and are transmitted from one individual to another.

Typhus is a very important disease which migrates with people, principally refugees. After the last war it was reported that approximately 10,000,000 people had typhus as a result of war conditions. The death rate is frequently very high. Large epidemics of typhus did occur in Egypt, and in Persia there was a small outbreak. We had reports that typhus had broken out in Tripoli, and when we captured that city we found some; but

again, by keeping the natives away from our troops or our troops away from the natives, by placing the infested part of cities out of bounds, preventing our troops from entering the infested areas or having contact with infected people, typhus can be prevented, and we didn't get any large number of cases of typhus among our troops.

Fortunately the United States of America Typhus Commission was in my theatre. It carried on extensive work on the efficacy of certain control measures among the native population. We believe that we have a very effective means of controlling typhus among our troops, and are most optimistic about the control of typhus. Epidemic typhus was found largely in Egypt; a mixture of epidemic and murine typhus in Eritrea and Ethiopia. Murine typhus prevailed in Syria where it is endemic; there was both epidemic and murine typhus in Persia and Iraq where it is also endemic. The entire Middle East may be regarded as an endemic area for typhus, either epidemic or murine typhus. We learned some very interesting things about typhus and I saw personally a good many hundred cases. This Commission studied also the clinical course of the disease, the complications and the pathology, and their findings will be published later.

Yellow fever is another disease of importance. The yellow fever belt extends across Central Africa to the Red Sea. The disease has migrated from the west coast to the east as a result of religious pilgrimages to Mecca, and we were very much interested in the possibility of an outbreak of yellow fever in Eritrea, which would have been a serious thing for American forces there. The *Aedes aegypti* were found there in large numbers.

Dr. Mahaffey, who has done so much work in Africa [with the Rockefeller Commission] on yellow fever, was brought in to Eritrea, and he obtained many blood samples from natives. Mouse protection tests were done, and it was found that yellow fever had been present in Eritrea. Very strict precautions were therefore required. Quarantine regulations were placed into effect in the spraying of planes going into uninfected areas in the Middle East, from the yellow fever areas and the potential yellow fever areas. We have a very efficient vaccine now for yellow fever, and it has been widely publicized that our troops going into such areas have been inoculated. We are happy to report we have had no yellow fever cases among our troops. However, that does not in any way permit a relaxation of vigilance so long as our aircraft travel through the yellow fever belt, and passengers, who of course include other than military personnel who have been inoculated, go into and out of that area. There is the ever present danger of infected mosquitoes being transported by air into non-endemic areas and causing foci of yellow fever to develop in various parts of this world. We kept a very close watch on the spread of yellow fever.

Plague, like most of these tropical diseases, is also carried by an insect, in this case by the rat flea. An epidemic of plague in the Middle East itself was observed to migrate from an initial focus in one port to four different widely separated ports, as a result of infected rats boarding these ships and

then infecting other rats at the other ports. The fleas left the dead bodies of the rats which died of the disease, got on human beings and infected them, and they died of bubonic plague. These certain cities were placed completely out of bounds as far as American troops were concerned. An investigation of the epidemic showed that it was the pneumonic type with 100 per cent mortality in the particular ports in which the epidemic occurred.

Infectious hepatitis is another very interesting disease which is endemic throughout the Middle East, particularly in the Levant and along the northern coast of Africa. It was a very important disease because if it strikes troops in large numbers those troops are unable to fight. It not only affected our own troops but those of our enemy. Many Germans and Italians were left to be prisoners because they were too ill with infectious hepatitis to be moved.

In the Levant, infectious hepatitis was sometimes called the "immigrant disease" because people coming into that country almost universally become infected. Much remains to be learned about the disease. The mode of transmission is not known, whether it is transmitted by means of flies or by a blood-sucking insect such as the mosquito, or perhaps the sand fly. It is known that the virus is in the blood, particularly in the preicteric stage, and that it can be transmitted to others by direct inoculation of the blood. The incubation period is extremely variable, from two weeks to three or four months, as has been determined by inoculation experiments. It is known, too, that individuals may carry the virus in their blood and, as far as known, not develop the symptoms until a precipitating factor occurs, such as fatigue or reduced rations. In general, lowered resistance to any type of infection may precipitate the clinical symptoms in individuals who have been carrying the virus for long periods of time. The initial symptoms are usually anorexia and a resulting loss of weight. Then jaundice develops, and there is usually nausea and vomiting. There may be hematemesis, delirium and mental confusion. There is an appreciable death rate. The period of hospitalization on the average is relatively long, from four to six weeks, and that is an important factor in a military organization, particularly if a relatively large number of troops develops infectious hepatitis during an epidemic. Among our troops the disease was observed in all degrees of severity from the mildest infection with only anorexia and a slight icteric tinge to quite severe cases who required a long period for convalescence. The treatment used was a high carbohydrate high vitamin B diet. A study has been made of the epidemiology of one outbreak and a commission has been working on the problem of how this disease is transmitted because the answer to that problem will enable us to control it. Epidemiological observations together with the fact that the virus is present in the blood and can be transmitted by direct inoculation lead me to believe that it is borne by blood-sucking insects, possibly mosquitoes or sand flies. I rather suspect the *Aedes aegypti* because after an unusual so-called wind-borne flight of these mosquitoes into an area in which certain troops were located, an outbreak of infectious



heat stroke very low. Heat prostration is very common, and we were able to control that largely by the use of salt.

Particularly interesting are the effects of prolonged exposure; that is, of being exposed to this heat for months at a time. I will describe briefly a few of the changes that take place. In an effort to get rid of body heat, the capillary beds and superficial blood vessels are dilated more or less continuously, and after a period of some months an apparent anemia develops; that is, a red cell count of three to three and a half million cells is normal. This is not due to a decrease in red cell production but to an increase of plasma, and the old idea of your "blood becoming thinned out in the tropics" is literally true. Also a hypotension becomes the rule. Individuals with hypertension with a systolic pressure up to 250 millimeters frequently show a fall to 135 or 140 millimeters. An individual who has a normal systolic pressure of 120 to 130 mm. frequently has a pressure scarcely reaching 100 millimeters of mercury after a few months. The diastolic pressure is only slightly lowered.

After some months of exposure, the development of these changes in the blood count and in the blood pressure results in the appearance of certain symptoms. These are the symptoms which might be expected with cerebral anemia or arteriosclerosis. The individuals become very irritable, they quarrel and fight over the slightest imagined insult; they become extremely forgetful, and I have seen individuals start out to see someone and forget whom they are going to see. It becomes almost a rule that you must write down everything in a notebook if you are to remember it longer than five minutes. Accompanying this irritability and forgetfulness, the inability to concentrate on a problem becomes very marked. Men complain that they are unable to do their work because they can't concentrate on it. There is nothing particularly new in this syndrome. However, few doctors recognize it as a clinical entity.

There is also a lowered resistance to all types of infection. The slightest scratch becomes a chronic sore. The infection rate of respiratory diseases, strange to say, is very high. These changes are not particularly new and have been studied by many others, but they are becoming increasingly important because for the first time in history we have large numbers of American physicians in these areas, where the prolonged exposure to the effects of heat must be dealt with. Those of you who are in teaching institutions, might advantageously present these changes, this clinical entity, if you care to call it that, to those students who may in the near future join the armed forces and be sent out to these areas, where they are to meet this problem. I first became interested in the disease myself from 1937 to 1939, when I made studies in Panama in an effort to determine the cause of a very high rate of respiratory infection there. I found it was due to the effects of heat. It is well to recognize that not all diseases, not all clinical entities are the direct result of infection, and that the effects of prolonged exposure to heat are as much a clinical entity as any other of the better known diseases,

such as vitamin deficiencies and metabolic diseases. It deserves the thought and scientific study of our internists, particularly in order that we may recognize that such a condition exists and establish certain criteria so that, if possible, individuals may be removed from prolonged exposure to heat before permanent damage is done. We might well call this clinical entity the "heat syndrome." It has no relation whatsoever to heat stroke or heat prostration which have been studied so thoroughly.

I have touched very briefly on some of the medical problems that I encountered as Chief Surgeon of the United States Army Forces in the Middle East over a period of two years. From a medical standpoint, as applied to military forces, the most important problems were the intestinal diseases, principally the dysenteries, both bacillary and amebic. Sand fly fever, infectious hepatitis, and in certain areas malaria, and the "heat syndromes," were also very important problems. Some of the problems that we feared as the result of our first statistical survey of the area, particularly the exotic tropical diseases, did not materialize, as far as becoming problems to our military forces. The young men who will graduate from our medical schools during the next few years and who are going to be sent all over the world and who will encounter these unfamiliar diseases need guidance and special efforts to prepare them to recognize, to control and to treat them. To those who are primarily interested in research, I present the problems of sand fly fever, infectious hepatitis and the "heat syndrome," all of which challenge our best efforts in scientific study.

# HETEROPHILE ANTIBODY REACTION IN INFECTIOUS MONONUCLEOSIS \*

By ROBERT E. KAUFMAN, CAPTAIN, MEDICAL CORPS, A. U. S.

THE sheep cell agglutination test or heterophile antibody reaction, as it is also called, is a laboratory procedure of considerable value in clinical medicine. In this country one frequently speaks alternately of the Paul-Bunnell test; and in Europe it is often referred to as the Hanganutziu-Deicher reaction. In 1911 Forssman<sup>1</sup> recognized the nonspecificity of certain antigen-antibody reactions. The terms "heterogenetic," "heterophilic," or "heterophile" are applied to those antibodies that react with an antigen (sheep erythrocytes) which seemingly had nothing to do with their development. One type of heterophile antibody is known as the Forssman antibody, but there are other varieties of heterophile antibodies which differ from the Forssman type. It has been known for a long time that the serum of many normal persons is able to clump sheep erythrocytes in very low dilutions.<sup>2</sup> In 1924 Hanganutziu<sup>3</sup> noted high titers of heterophile antibodies in the sera of patients who had received injections of horse serum. These observations were confirmed two years later by Deicher.<sup>4</sup> Davidsohn,<sup>5, 6, 7</sup> in a series of publications, reported many more such instances, and further showed that the titer of heterophile antibodies is especially high if the horse serum injection is followed by serum disease.

During the course of a search for heterophile antibody responses in various clinical conditions, Paul and Bunnell<sup>8</sup> in 1932 discovered a high titer of such antibodies in the sera of several patients with infectious mononucleosis. Bunnell<sup>9</sup> later showed that this occurred in most cases of the disease and that it was sufficiently characteristic to be useful as a diagnostic aid. Numerous subsequent clinical reports<sup>10, 11, 12, 13, 14, 15, 16, 17</sup> emphasize the confirmative value of the sheep cell agglutination test in the diagnosis of infectious mononucleosis. Many investigations<sup>18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29</sup> have been conducted in the laboratories of Davidsohn, of Stuart, and of others, which ultimately proved that the heterophile antibodies in infectious mononucleosis were different in type from those found in normal serum and in the serum of patients who had received horse serum injections. The present concept is that there are three types of sheep cell agglutinins: those in normal serum, absorbed by guinea-pig kidney but not by beef erythrocytes; those in the serum of patients with infectious mononucleosis, absorbed by beef erythrocytes but not by guinea-pig kidney; and those in the serum of

\* Received for publication July 31, 1943.

From the Lenox Hill Hospital, New York City.

Acknowledgment is made to Dr. Annis E. Thomson of the Bureau of Laboratories, Department of Health, City of New York, for devising the technic of the heterophile antibody reaction used in this series of cases and for the performance of the serological tests.

individuals treated with horse serum, absorbed by both guinea-pig kidney and beef erythrocytes.<sup>17</sup>

Various modifications<sup>12, 23, 30, 31, 32, 33</sup> of the Paul-Bunnell test have been suggested in order to make the test more rapid or more sensitive. Whereas the Paul-Bunnell method requires overnight incubation before final reading, the newer Davidsohn technic,<sup>31, 32</sup> which is very delicate, makes use of smaller amounts of material and requires only two hours' incubation. The Paul-Bunnell and the Davidsohn methods are the two standard procedures in this country at the present time. The differential test of Davidsohn consists of three parts: (a) agglutinating action of the patient's serum on sheep cells; (b) the same after absorbing the heterophile antibody with guinea-pig kidney; (c) the same after absorbing with beef erythrocytes. Thus, a typical result in a case of infectious mononucleosis would be reported as follows: "(a) serum, non-absorbed 1:448; (b) serum absorbed with guinea-pig kidney 1:224; (c) serum absorbed with boiled beef erythrocytes: no agglutination."

#### TECHNIC

Practically every experienced laboratory worker who performs many sheep cell agglutination tests has made certain minor modifications in the recognized technics. Dr. Annis E. Thomson has done over 2000 of these tests by the Davidsohn method,<sup>31, 32</sup> unmodified until October, 1939, since which time the following changes have been in effect. First, instead of inactivating the serum for 30 minutes at 56° C., it was inactivated for four minutes at 61° C. Second, instead of reading the results of the agglutination after incubating for two hours at room temperature and again after overnight in the icebox, the final results were read after centrifuging at high speed for five minutes and then shaking thoroughly with the fingers. A carefully controlled series of tests showed that the two methods give essentially similar results. Third, instead of absorbing sera for one hour, five minutes were found to be sufficient, if the tubes were shaken thoroughly during that time. This applies to both the guinea-pig kidney and the beef erythrocytes. Fourth, the expressions "one plus," "two plus," and "three plus" are not used; merely "positive" or "negative." Fifth, all results were read macroscopically, because after centrifugation there was not enough diagnostic difference to warrant the use of the microscope. The net result of these minor changes in Davidsohn's standard technic is that the test is simplified, is just as accurate, and withal gives considerably quicker results. In fact, telephoned reports can be given within one hour of the time of arrival of the serum in the laboratory, if speed of diagnosis is important, which it occasionally is in a questionable case of infectious mononucleosis thought to be acute appendicitis, meningitis, typhoid fever, mumps, diphtheria, etc. Moreover, so much time is saved by these modifications in technic that many more specimens can be examined in a day. A complete description of the technic will soon be published.<sup>34</sup>

TABLE I

## Infectious Mononucleosis

In each case the agglutinin titers reported are (1) with untreated serum; (2) with serum after absorption with guinea pig kidney; and (3) with serum after absorption with boiled ox erythrocytes.

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd-5th Day	6	7	8	9	10	11	12th-15th	16th-21st	22nd-30th	1-2 Mos.	2-3 Mos.	3-4 Mos.	4-6 Mos.	6-9 Mos.	9-12 Mos.
1	M	17	Neg.										Neg.				1:112 1:56 Neg.	9-12 Mos.
2	M	14						1:14 N.D. N.D.				1:28 N.D. N.D.						
3	M	41										1:56 N.D. N.D.						
4	F	27				1:16				1:64								
5	M	25	1:112 1:28 Neg.					1:112 1:28 1:14										
6	M	22							1:32				1:448 1:224 Neg.			1:112 1:28 Neg.		Neg.
7	M	14						Neg.				Neg.				1:56 1:28 Neg.		
8	F	11										1:28 N.D. N.D.	1:224 1:56 Neg.			1:14 Neg. Neg.		
9	M	17						1:56 1:7 Neg.					1:112 1:56 Neg.				1:14 Neg. Neg.	
10	F	23						1:112 1:56 Neg.										
11	M	33						Neg.				1:224 1:56 Neg.				1:112 1:14 1:14	1:28 1:14 Neg.	

TABLE I—Continued

Case No.	Sex	Age	3rd-5th Day	6	7	8	9	10	11	12th-15th	16th-21st	22nd-30th	1-2 Mos.	2-3 Mos.	3-4 Mos.	4-6 Mos.	6-9 Mos.	9-12 Mos.
12	M	31		1:56 1:14 Neg.			1:112 N.D. Neg.								1:28 Neg. Neg.			
13	F	31							1:112 N.D. Neg.			1:224 N.D. Neg.						
14	F	13																
15	M	1		Neg.						1:28 1:14 N.D.						1:224 1:112 1:7	1:112 Neg. 1:56	
16	F	24	1:112 1:28 Neg.						1:112 1:14 Neg.									
17	F	34	1:14 Neg. 1:14				1:112 1:56 1:7								1:56 1:28 Neg.			
18	M	27							Neg.		1:112 1:28 Neg.							
19	M	17		1:112 Neg. Neg.				1:7 Neg. Neg.				1:14 Neg. Neg.						1:7 Neg. Neg.
20	M	30		1:112 1:28 Neg.				1:56 1:14 Neg.										
21	M	42			1:112 Neg. Neg.		1:112 1:56 1:14									1:28 Neg. Neg.		
22	F	31							Neg.			1:28 1:14 Neg.						
23	M	3							1:112 Neg. Neg.		1:112 Neg. Neg.							

TABLE I—Continued

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd-5th Day	6	7	8	9	10	11	12th-15th	16th-21st	22nd-30th	1-2 Mos.	2-3 Mos.	3-4 Mos.	4-6 Mos.	6-9 Mos.	9-12 Mos.
24	F	5																
25	F	2																
26	M	7																
27	F	41																
28	F	45	1:28 1:14 Neg.					1:14 Neg. Neg.						1:28 Neg. Neg.				
29	M	36																
30	F	32																
31	F	13												1:56 Neg. Neg.				
32	M	25																
33	F	22						1:56 1:14 Neg.						1:28 Neg. Neg.	1:56 1:14 Neg.		1:14 Neg. Neg.	
34	F	27							1:1792 1:1792 Neg.					1:112 1:112 Neg.			1:28 1:14 Neg.	1:28 Neg. Neg.
35	M	29									1:28 1:14 Neg.							

TABLE I—Continued

Time of Test After Onset of Disease																		
Case No.	Sex	Age	3rd-5th Day	6	7	8	9	10	11	12th-15th	16th-21st	22nd-30th	1-2 Mos.	2-3 Mos.	3-4 Mos.	4-6 Mos.	6-9 Mos.	9-12 Mos.
36	M	14					1:28 1:14 Neg.											
37	M	12									1:56 1:28 Neg.							
38	M	2									1:32	1:28 Neg. Neg.	1:112 Neg. 1:56	1:28 Neg. 1:28	1:56 1:7 Neg.			
39	M	30																
40	M	5											1:28 Neg. Neg.					
41	F	21			1:224 1:112 Neg.													1:14 Neg. Neg.
42	F	28			1:56 1:14 Neg.					1:1792 1:1792 Neg.	1:3584 1:1792 Neg.	1:3584 1:1792 Neg.	1:896 1:448 Neg.		1:112 1:28 Neg.	1:56 1:14 Neg.		
43	M	28									1:56 1:14 Neg.		1:56 1:28 Neg.			1:7 Neg. Neg.		
44	M	13									1:448 1:224 Neg.				1:7 Neg. Neg.			
45	F	3											Neg.					
46	M	4					1:28 1:14 Neg.					1:28 Neg. Neg.						
47	F	6								1:28 Neg. Neg.								
48	F	27										1:56 1:28 Neg.						



TABLE I—Continued

Time of Test After Onset of Disease																		
Case No.	Sex	Age	3rd-5th Day	6	7	8	9	10	11	12th-15th	16th-21st	22nd-30th	1-2 Mos.	2-3 Mos.	3-4 Mos.	4-6 Mos.	6-9 Mos.	9-12 Mos.
49	M	27	1:14 Neg. Neg.				1:14 Neg. Neg.			1:28 Neg. Neg.	1:7 Neg. Neg.							
50	F	30						1:28 Neg. 1:7				Neg.	1:56 1:14 Neg.					
51	F	10								1:14 1:14 Neg.		1:28 Neg. Neg.	1:28 Neg. Neg.					
52	M	8											1:7 Neg. Neg.					
53	F	19	1:14 Neg. Neg.	1:28 1:14 Neg.			1:112 Neg. Neg.											
54	M	9																
55	F	17	1:56 Neg. 1:56				1:28 Neg. Neg.											
56	F	15								1:7 Neg. Neg.	1:28 Neg. Neg.							
57	M	33	1:28 Neg. Neg.	1:28 1:14 Neg.					1:56 Neg. Neg.				1:28 Neg. Neg.	1:7 Neg. Neg.				
58	F	20								1:14 Neg. Neg.								
59	M	46																
60	M	12	Neg.											1:56 Neg. Neg.				
61	M	12							Neg.		Neg.		Neg.		Neg.			

TABLE I—Continued

[illegible]

TABLE I—Continued

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd-5th Day	6	7	8	9	10	11	12th-15th	16th-21st	22nd-30th	1-2 Mos.	2-3 Mos.	3-4 Mos.	4-6 Mos.	6-9 Mos.	9-12 Mos.
76	F	8		1:7 Neg. Neg.							1:7 Neg. 1:7	1:7 Neg. Neg.	1:7 Neg. Neg.					
77	F	52											1:7 Neg. Neg.					
78	F	25	1:7 Neg. Neg.				1:7 Neg. Neg.					1:7 Neg. Neg.						
79	F	21			1:7 Neg. Neg.				1:7 Neg. Neg.			1:28 Neg. Neg.		1:14 Neg. Neg.				
80	F	27																
81	F	15												1:14 Neg. Neg.	1:56 1:14 Neg.	1:7 Neg. Neg.		
82	M	30										1:448 1:448 Neg.	1:448 1:448 Neg.	1:112 1:56 Neg.	1:14 Neg. Neg.			
83	F	25	1:56 1:14 Neg.						1:14 Neg. Neg.		1:112 1:28 Neg.		1:448 1:224 Neg.					

TABLE II  
Control Series

In each case the agglutinin titers reported are (1) with untreated serum; (2) with serum after absorption with guinea pig kidney; and (3) with serum after absorption with boiled ox erythrocytes.

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
Leukemia and Lymphoblastoma				
1	F	59	Neg. Neg. Neg.	Leukemia, chronic myeloid
2	M	58	Neg. Neg. Neg.	Leukemia, chronic myeloid
3	F	59	1:28 Neg. 1:28	Leukemia, chronic myeloid
4	F	57	1:14 Neg. Neg.	Leukemia, chronic myeloid
5	M	17	Neg. Neg. Neg.	Leukemia, chronic lymphoid
6	F	4	Neg. Neg. Neg.	Leukemia, acute lymphoid
7	M	46	Neg. Neg. Neg.	Leukemia, chronic myeloid
8	M	20	1:14 Neg. Neg.	Hodgkin's disease
9a	M	30	1:112 1:28 Neg.	Hodgkin's disease
9b	M	30	1:224 Neg. 1:56	Nine months later
10a	M	45	1:14 Neg. 1:7	Hodgkin's disease (?)
10b	M	45	1:112 Neg. 1:56	One week later
11	F	69	1:7 Neg. Neg.	Lymphosarcoma

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
Serum Injections				
12	F	3	1:28 Neg. Neg.	Scarlet fever, 12 days after serum
13	F	10	1:14 Neg. Neg.	Scarlet fever, 11 days after serum
14	M	8	1:112 1:56 Neg.	Scarlet fever, 10 days after serum
15	M	11	1:14 Neg. 1:7	Scarlet fever: serum sickness
16	M	13	1:7 Neg. Neg.	Scarlet fever: serum sickness
Liver Extract Injections				
17	F	63	1:7 Neg. Neg.	Primary anemia
18	M	67	Neg. Neg. Neg.	Primary anemia
19	M	55	1:28 Neg. Neg.	Primary anemia
20	F	46	1:7 Neg. Neg.	Primary anemia
21	F	67	1:28 Neg. Neg.	Primary anemia
22	F	55	1:28 Neg. 1:7	Primary anemia
23a	F	33	1:112 Neg. Neg.	Primary anemia
23b	F	33	1:14 Neg. Neg.	Three weeks later

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
Respiratory Infections				
24	F	45	1:14 1:14 Neg.	Grippe
25	M	31	1:7 Neg. Neg.	Grippe
26	M	44	Neg. Neg. Neg.	Grippe
27	F	40	1:14 1:14 Neg.	Grippe
28	M	53	1:7 1:14 Neg.	Grippe
29	M	30	1:14 Neg. Neg.	Grippe
30	M	?	Neg. Neg. Neg.	Grippe
31	M	15	1:14 Neg. Neg.	Grippe
32	M	45	1:14 Neg. Neg.	Grippe
33	M	20	1:28 Neg. Neg.	Grippe
34	F	15	Neg. Neg. Neg.	Grippe
35	F	48	1:28 Neg. 1:28	Acute tonsillitis
36	M	46	1:14 Neg. Neg.	Asthma
Miscellaneous Diseases				
37	M	30	Neg. Neg. Neg.	Pulmonary tuberculosis

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
<i>Miscellaneous Diseases—Continued</i>				
38	M	20	1:28 Neg. Neg.	Undulant fever
39	M	?	Neg. Neg. Neg.	Trichiniasis (?)
40	M	35	1:28 Neg. Neg.	Rheumatic fever (?)
41	F	23	Neg. Neg. Neg.	Pyelitis, acute
42	M	42	1:28 1:7 Neg.	Syphilis; cholecystitis, acute
43	F	64	Neg. Neg. Neg.	Vitamin B deficiency
44a	M	19	1:56 Neg. Neg.	Rubella
44b	M	19	1:14 Neg. Neg.	Five days later
<i>Healthy Normals</i>				
45	M	23	Neg. Neg. Neg.	
46	F	58	1:7 Neg. Neg.	
47	M	48	1:28 Neg. Neg.	
48	F	42	1:28 1:7 Neg.	
49	F	18	1:14 Neg. Neg.	
50	F	19	1:28 Neg. Neg.	

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
Healthy Normals— <i>Continued</i>				
51	F	18	1:28 Neg. Neg.	
52	F	20	1:14 Neg. Neg.	
53	F	19	1:7 Neg. Neg.	
54	F	18	1:14 Neg. Neg.	
55	F	19	1:28 Neg. Neg.	
56	F	19	1:7 Neg. Neg.	
57	F	18	1:7 Neg. Neg.	
58	F	20	1:28 Neg. Neg.	

## CLINICAL

During a three year period 83 proved cases \* of infectious mononucleosis have been investigated and are included in this paper. In the diagnosis of this disease there are three aspects to consider: the clinical, the hematological, and the serological. It is felt that if any two of them are definite, the diagnosis may be considered established. In this series were seen no cases positive clinically and serologically, but with consistently negative blood smears. However, there were many cases positive clinically and hematologically, but with negative serological findings, and a few cases positive hematologically and serologically, but with a subclinical or a very atypical clinical picture. The clinical and hematological aspects of infectious mononucleosis will not be discussed in this paper, since little could be added to Bernstein's excellent and exhaustive review.<sup>17</sup>

Sheep cell agglutination tests were done on the sera of all but five of our

\* I wish to thank the following physicians for referring some of these patients for study: Drs. Abram Abelloff, Charles Bogoshian, Frederick Castrovinci, Lawrence Crawley, Carl Goldmark, Jr., Irving Kohn, George Laporte, Jr., Carl Reich, Armin St. George, Robert Schleussner, Nathan Serlin, and Irwin Sobel.



83 patients by Dr. Thomson.\* The Paul-Bunnell technic was employed for one patient (case 4), and four patients (cases 71, 72, 73, 75) had no serological tests performed. I studied the blood smears of all 83 patients and also examined the patients with but few exceptions. In the cases not personally examined, the histories as reported by other doctors were carefully reviewed.

We were interested in performing the heterophile antibody reaction as frequently as was feasible in order to determine the variations in the titer with time. The results of these tests are shown in table 1. Also included is a control series (table 2), consisting of normal individuals; patients who had received liver extract injections for primary anemia; patients who had received horse serum for diphtheria or scarlet fever; and patients suffering from serum sickness, leukemia, Hodgkin's disease, and various miscellaneous conditions.

### DISCUSSION

What titer of heterophile antibody constitutes a positive test? That depends on various factors, the most important of which is the exact technic employed, including the method of reading the result, whether macroscopic or microscopic; the time interval, whether after two hours or after overnight incubation or after five minutes centrifugation; and the method of recording the degree of the reaction, "one plus" or "three plus" agglutination. It also depends on how one records the dilution. The differences in the dilutions of serum recorded in various publications make it very difficult to compare titers with each other. For example, Paul and Bunnell<sup>8</sup> call their first tube 1:4 (whereas it is in reality a 1:16 dilution of serum); Davidsohn<sup>31</sup> designates his first tube 1:7; and Bernstein<sup>11</sup> his first tube 1:20. Finally, another consideration seems to be the opinion of the author, based on his technic and experience. The lowest figure which may be called positive varies with different writers on this subject from 1:8<sup>10</sup> through 1:32,<sup>8, 9, 11, 16, 17, 35</sup> 1:56,<sup>31, 35, 36</sup> 1:64,<sup>37, 38</sup> 1:320,<sup>23</sup> up to 1:512.<sup>39</sup> It should be pointed out that the extreme figures (1:8, 1:320, 1:512) were obtained with technics not now in general use. The two methods in common use in this country are the Paul-Bunnell and the Davidsohn. Most authors follow the originators of these methods in calling the lower level of positivity 1:32 with the former and 1:56 with the latter technic. The latter figure is considered positive by Davidsohn and most others only if the differential absorption is "correct"; i.e., if there is little absorption of heterophile antibody with guinea-pig kidney and complete absorption with beef erythrocytes.

From our experience and a review of the literature, we agree with Demanche<sup>14</sup> that the borderline between negative and positive cannot be very definitely stated. There are too many variable factors even with the well

\*Dr. Thomson has performed the test on the sera of a great many other patients with infectious mononucleosis; but these cases are not included in this paper as they were not studied clinically and hematologically by me.

recognized technics, especially since most investigators have varied the technic in some particulars. If definite figures are to be given, however, we feel with many others that with the Paul-Bunnell technic a value of 1:32 or more is positive, and we would add that 1:16 is suggestive, requiring further investigation. We consider that with the Davidsohn technic, especially as modified by us, 1:56 or more is positive and even 1:28, provided that in the latter instance the differential absorption is "correct." The figures for the Davidsohn method refer to the macroscopic reading after overnight incubation in the icebox or, as we now do it, after centrifugation for five minutes. Smeall,<sup>40</sup> using the Paul-Bunnell technic, found only 0.4 per cent of 765 normal sera with an agglutination above 1:32.

With borderline results, the clinical and hematological features should be taken into consideration. Even with definitely positive sheep cell agglutination tests, the clinical picture must be considered as a whole in making a final diagnosis in an individual case. There are false-positives with this test just as with other laboratory procedures, such as the serological reactions for syphilis,<sup>41</sup> which are usually considered quite dependable. Among other things which must be known in interpreting a borderline or positive test in connection with the patient's present illness is whether he had recently been given serum or liver extract injections and whether he may have had infectious mononucleosis at any time within the past 12 months in clinical or even subclinical form.

With the foregoing limitations, a positive sheep cell agglutination test naturally is a strong point in the diagnosis of infectious mononucleosis, especially if the agglutination occurs in a high dilution and with the "correct" differential. However, as table 1 shows and as others<sup>16, 17, 42, 43, 44</sup> have also found, a negative test does not by any means rule out the diagnosis, even if the test is repeatedly negative. It is merely one point against the diagnosis; but if the clinical and the hematological pictures are definite, it is believed that the diagnosis is established. And we do not agree with Davidsohn<sup>31</sup> that it is necessary or desirable to separate seropositive from seronegative cases of what is considered to be the same disease.

The percentage of cases of infectious mononucleosis with negative sheep cell agglutination tests varies a great deal in different series of reported cases. This depends mainly on three factors: (a) the figure which the author considers necessary for a test to be called positive; (b) the frequency with which blood samples are tested in individual cases; (c) and most important, the number of cases of infectious mononucleosis which the author refuses to recognize and include as such because they have negative heterophile antibody reactions, even though they are "indistinguishable from infectious mononucleosis clinically and hematologically," in the words of certain authors. It is felt that these cases must be included in a discussion of the accuracy of the test. Van Ravenswaay,<sup>35</sup> for example, stated that all 16 of his cases of infectious mononucleosis had positive tests. However, 21 other

cases thought to be infectious mononucleosis before the agglutination test was performed were excluded because of negative tests. It would seem more correct to say that 16 of 37 cases or 43 per cent had positive reactions. Demanche<sup>14</sup> had 100 per cent positives in a series of 57 cases, but if seven other cases excluded only because of negative tests are included, his percentage falls to 89 per cent. The percentage of cases with positive agglutination tests varies in different series<sup>9, 10, 14-17, 35, 37, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53</sup> from 43 per cent to 100 per cent, with most authors reporting 80-90 per cent. Paul<sup>16</sup> said: "Ninety per cent of our cases had positive serology. This may indicate that we are relying too much upon the sheep cell test for our diagnosis." I agree with that interpretation.

In this series of 79 serologically tested cases we found that 51 were definitely positive (1:56 or more); eight were borderline (1:28 with the "correct" differential); and 20 were negative. Since we feel that 1:28 with the "correct" differential is also a positive test, our series shows 74.7 per cent positive cases. It is apparent from a glance at table 1 that the number of positive cases depends to some extent on when and how often one takes blood for the test. For example, one patient (case 7) was negative on the tenth and eighteenth days, but positive five months after the onset (with no intervening illness). In this series are included all cases in which we made a final diagnosis of infectious mononucleosis, whether the agglutination test was positive or negative. In fact, three children and one adult from whom blood was not obtainable are included, since the clinical and hematological pictures were very definite. This is correct, it is believed, especially since it happened that all three children had siblings ill at the same time with similar symptoms and blood smears and positive agglutination tests. I must admit that a few cases studied were excluded because of a negative test in the presence of clinical and hematological pictures which were suggestive but not entirely characteristic. These cases would have been included if the agglutination test had been positive. Since there are false-positive and false-negative sheep cell tests, and since the clinical and hematological pictures of infectious mononucleosis can be so variable, one must not be too dogmatic in any statements concerning this remarkable disease. Incidentally it should be noted that the titer of the sheep cell agglutinins bears no relation to the severity of the disease. Patients have been seen with reactions positive in dilutions of 1:1792 or 1:3584, although they were not ill enough to be kept in bed.

It is of clinical interest to know how soon in the disease the sheep cell agglutination test may become positive and how long it may remain so. In this series, one patient (case 16) had a definitely positive reaction as early as the third day of illness; one (case 55) on the fourth day; one (case 28) on the fifth day; and many others on the sixth day. Werlin, Dolgopoul and Stern<sup>30</sup> had one patient with a positive reaction on the second day of illness. Bernstein<sup>17</sup> found a strongly positive test on the third day in one patient,

as did McAlpin.<sup>54</sup> Friedemann and Beer<sup>10</sup> record a positive test on the fourth day in one patient; Worms and Demanche<sup>55</sup> in one; and Bunnell<sup>9</sup> in two. Positive reactions have frequently been seen on the fifth and sixth days.<sup>9, 15, 17</sup>

As illustrations of the fact that the sheep cell agglutination test may not become positive until late in the disease in certain cases, we may observe from table 1 that case 1 was negative on the forty-fifth day and positive when retested during the sixth month; case 7 was negative on the twentieth day and positive during the fifth month; case 8 was negative in the third week and positive in the fourth week; case 30 was negative on the sixteenth day and positive on the fortieth; and finally case 50 was negative on the thirtieth day and positive on the thirty-eighth. None of these patients had any illness intervening between the last negative and the first positive tests. Himsworth<sup>56</sup> reported a case with a negative Paul-Bunnell test on the thirtieth day and a positive test during the third month. Bernstein<sup>17</sup> suggests that if the agglutination reaction is not positive at the end of one month from the onset of symptoms one can consider that it will not become positive. Some of the cases in this series show that the time limit cannot be so definitely set.

The test may remain positive for a long time, as some of these cases show. Case 1 was still positive serologically at six months; case 11 at seven and 11 months; cases 16 and 42 at six months; and case 70 at about 12 months, although the last case should perhaps not be included as I had not followed the course of the illness, but made the diagnosis in retrospect. Davidsohn<sup>31</sup> found positive tests lasting at least as late as the third and fourth months in two cases; Demanche<sup>57</sup> as late as four and a half months; and Sohler, Parnet and Bernier<sup>49</sup> past the third month. Apparently we have found a few cases in which the agglutination test remained positive longer than had previously been considered the upper limit. It is important to know that this reaction may remain positive for many months, since when one performs the test as an aid in diagnosing a febrile illness, it may be positive not as a result of the present illness, but of an attack of infectious mononucleosis many months before. A confusing situation arose in the case of a three-year-old girl (case 70) with unexplained fever and blood smears very suggestive of infectious mononucleosis. The sheep cell agglutination test was twice positive, yet the clinical diagnosis proved to be pneumococcus bacteremia (probably secondary to a pneumonia). In going into the past history carefully, we discovered from her pediatrician that she had had an illness 11 or 12 months before, which, considered in retrospect, was probably infectious mononucleosis. This would explain the suggestive smears and the positive heterophile antibody reactions, both of which may be present for many months, even for almost a year.

In summary of this aspect of the problem, it may be said that the sheep cell agglutination test usually becomes positive between the sixth and twenty-

first days of the illness, although sometimes earlier and sometimes not until much later or not at all. It usually remains positive for two to four months after the onset of the disease, although this is very variable, and it may return to negative much sooner or not until much later. As a rule, a positive test will be found for a longer period of time if the reaction was at some time positive in a high dilution. If only one diagnostic venepuncture is to be done, such as in children or in uncoöperative adults, it would seem best to do this not earlier than the ninth day nor later than the thirtieth day, and preferably between the twelfth and twenty-first days.

The sheep cell agglutination test has considerable value in clinical medicine, especially in febrile illnesses in which the diagnosis is not entirely certain. We feel that the test should be performed in fevers of unknown origin; in acute throat infections in which the diagnosis is not perfectly clear, such as in cases suspected of having diphtheria but in whom virulent Klebs-Loeffler bacilli are not found<sup>50</sup>; in patients with acute or subacute lymphadenopathy, local or generalized; in persons found to have an unexplained leukocytosis or leukopenia with a relative lymphocytosis or monocytosis, who may or may not be ill; in cases diagnosed as leukemia; and in definite or suspected cases of infectious mononucleosis. Also, as Bernstein<sup>17</sup> points out, in individuals with positive agglutination tests (Widal, etc.) without cultural confirmation; patients with false-positive Wassermann or similar reactions; individuals with unexplained acute abdominal conditions; patients with enlarged spleens, puffy eyelids or atypical forms of conjunctivitis; apparent cases of catarrhal jaundice, purpura hemorrhagica, Vincent's infection, aphthous stomatitis, benign lymphocytic meningitis, granulocytopenia. I agree with Demanche,<sup>58, 59</sup> Durupt,<sup>60</sup> and Bernstein<sup>17</sup> that the test may be of great value in these conditions, especially if positive; but I also agree with Lyght<sup>61</sup> that "the diagnosis [of infectious mononucleosis] can usually be arrived at in advance of the aid promised by the agglutination procedure. If sheep cell agglutination tests are readily available, of course, they may be employed as clinching evidence." It must be remembered that a negative test does not rule out the diagnosis of infectious mononucleosis, and conversely that a positive test does not definitely establish this diagnosis. In cases suspected of having infectious mononucleosis, the test should be repeated at intervals, and if the titer rises or if the test becomes positive after having been negative, the diagnosis is established beyond doubt, provided the patient did not receive an injection of horse serum a short time before.

As table 2 illustrates, an increased heterophile antibody titer may occasionally be found after the administration of serum (case 14) or liver extract (case 23); and in cases in which the final diagnosis is something other than infectious mononucleosis (cases 9 and 44). Bernstein<sup>17</sup> and Kent<sup>62</sup> record a few other instances of false-positive reactions. No explanation can be given for these false-positive reactions. In patients suspected of having leukemia, especially the acute form, the physician may save himself con-

siderable embarrassment by having a sheep cell agglutination test performed routinely before giving the family a fatal prognosis, as occasionally what was thought to be leukemia is later recognized as infectious mononucleosis when the serological test is reported positive (which it practically never is in leukemia) and when the patient makes a complete recovery.

### CONCLUSIONS

1. Changes in Davidsohn's technic of performing the sheep cell agglutination test are described.
2. Tests were performed on 78 of 83 cases of infectious mononucleosis.
3. It is believed that agglutination in a dilution of 1:28 with the "correct" differential absorption tests is a positive reaction.
4. A positive test supports the diagnosis of infectious mononucleosis, but a negative test does not rule it out.
5. In this series, 75 per cent of the cases had positive reactions.
6. The reaction may become positive as early as the third day, but sometimes not until the second month or not at all.
7. The reaction usually remains positive for two to four months, although it may be nine to 12 months.
8. The test has considerable clinical value, especially if repeated at intervals in fevers of unknown origin.

### BIBLIOGRAPHY

1. FORSSMAN, J.: Die Herstellung hochwertiger spezifischer Schafhämolysine ohne Verwendung von Schafblut, *Biochem. Ztschr.*, 1911, xxxvii, 78.
2. DAVIDSOHN, I.: Heterophile antigens and antibodies, *Arch. Path. and Lab. Med.*, 1927, iv, 776.
3. HANGANUTZIU, M.: Hémagglutinines hétérogénétiques après injection de sérum de cheval, *Compt.-rend. Soc. de biol.*, 1924, ii, 1457.
4. DEICHER, H.: Über die Erzeugung heterospezifischer Hämagglutinine durch Injektion artfremden Serums, *Ztschr. f. Hyg. u. Infektionskr.*, 1926, cvi, 561.
5. DAVIDSOHN, I.: Heterophile antibodies in serum sickness, *Jr. Immunol.*, 1929, xvi, 259.
6. DAVIDSOHN, I.: Further studies on heterophilic antibodies in serum sickness, *Jr. Immunol.*, 1930, xviii, 31.
7. DAVIDSOHN, I.: Heterophilic antibodies in serum disease: Third Report, *Jr. Infect. Dis.*, 1933, liii, 219.
8. PAUL, J. R., and BUNNELL, W. W.: The presence of heterophile antibodies in infectious mononucleosis, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 90.
9. BUNNELL, W. W.: A diagnostic test for infectious mononucleosis, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 346.
10. FRIEDEMANN, V., and BEER, P.: Die Hanganutziu-Deichersche Reaktion bei der Angina mit mononukleärer Reaktion (Monozytenangina), *Deutsch. med. Wchnschr.*, 1933, lix, 440.
11. BERNSTEIN, A.: Antibody responses in infectious mononucleosis, *Jr. Clin. Invest.*, 1934, xiii, 419.
12. BUTT, E. M., and FOORD, A. G.: The heterophile antibody reaction in the diagnosis of infectious mononucleosis, *Jr. Lab. and Clin. Med.*, 1935, xx, 538.
13. DAVIDSOHN, I.: Infectious mononucleosis, *Am. Jr. Dis. Child.*, 1935, xlix, 1222.

14. DEMANCHE, M. R.: Le séro-diagnostic de la mononucléose infectieuse, *Sang*, 1938, xii, 86.
15. FOORD, A. G., and BUTT, E. M.: The laboratory diagnosis of infectious mononucleosis, *Am. Jr. Clin. Path.*, 1939, ix, 448.
16. PAUL, J. R.: Infectious mononucleosis, *Bull. New York Acad. Med.*, 1939, xv, 43.
17. BERNSTEIN, A.: Infectious mononucleosis, *Medicine*, 1940, xix, 85.
18. DAVIDSOHN, I., and WALKER, P.: The nature of the heterophile antibodies in infectious mononucleosis, *Am. Jr. Clin. Path.*, 1935, v, 455.
19. BAILEY, G. H., and RAFFEL, S.: Hemolytic antibodies for sheep and ox erythrocytes in infectious mononucleosis, *Jr. Clin. Invest.*, 1935, xiv, 228.
20. BEER, P.: The heterophile antibodies in infectious mononucleosis and after the injection of serum, *Jr. Clin. Invest.*, 1936, xv, 591.
21. KEMP, H. A., and BAKER, B. O.: On the behavior of the heterophile antibody (hemagglutinin) of serum sickness and acute infectious mononucleosis to absorption with raw and autoclaved ox erythrocytes, *Am. Jr. Clin. Path.*, 1936, vi, 560.
22. DAVIDSOHN, I.: Isoagglutinin titers in serum disease, in leukemias, in infectious mononucleosis, and after blood transfusions, *Am. Jr. Clin. Path.*, 1938, viii, 179.
23. STUART, C. A., BURGESS, A. M., LAWSON, H. A., and WELLMAN, H. E.: Some cytologic and serologic aspects of infectious mononucleosis, *Arch. Int. Med.*, 1934, liv, 199.
24. STUART, C. A., TALLMAN, J., and ANDERSON, E. G. E.: Agglutinins for sheep and rabbit erythrocytes in human sera, *Jr. Immunol.*, 1935, xxviii, 75.
25. STUART, C. A., TALLMAN, J., and BRINTZENHOFF, E.: Sheep and rabbit cell agglutinins in horse serum sickness and infectious mononucleosis, *Jr. Immunol.*, 1935, xxviii, 85.
26. STUART, C. A.: Heterophile antibodies in infectious mononucleosis, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxii, 861.
27. STUART, C. A., FULTON, M., ASH, R. P., and GREGORY, K. K.: The relations between certain heterophile antibodies and antigens, *Jr. Infect. Dis.*, 1936, lix, 65.
28. STUART, C. A., GRIFFIN, A. M., FULTON, M., and ANDERSON, E. G. E.: Nature of the antibodies for sheep-cells in infectious mononucleosis, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 209.
29. STUART, C. A., WELCH, H., CUNNINGHAM, J., and BURGESS, A. M.: Infectious mononucleosis, *Arch. Int. Med.*, 1936, lviii, 512.
30. STRAUS, R.: Simple slide and tube tests for infectious mononucleosis, *Am. Jr. Clin. Path.*, 1936, vi, 546.
31. DAVIDSOHN, I.: Serologic diagnosis of infectious mononucleosis, *Jr. Am. Med. Assoc.*, 1937, cviii, 289.
32. DAVIDSOHN, I.: Test for infectious mononucleosis, *Am. Jr. Clin. Path.*, 1938, viii, 56.
33. HOLLANDER, A.: The centrifuge technique in the heterophile agglutination test, *Jr. Lab. and Clin. Med.*, 1940, xxv, 542.
34. THOMSON, ANNIS E.: A rapid test for heterophile antibody in infectious mononucleosis—modified from Davidsohn's method, to be published.
35. VAN RAVENSWAAY, A. C.: The heterophile agglutination test in the diagnosis of infectious mononucleosis, *New England Jr. Med.*, 1934, ccxi, 1001.
36. BALGAIRIES, E., and CHRISTIAENS, L.: Le séro-diagnostic de la mononucléose infectieuse, *Paris méd.*, 1939, cxi, 493.
37. BOVERI, R.: Über das Vorkommen heterophiler Antikörper bei lymphoidzelliger Angina, *Klin. Wchnschr.*, 1933, xii, 666.
38. KRISTENSEN, M.: Studies on the serologic diagnosis of infectious mononucleosis, *Acta path. et microbiol. Scandinav.*, 1938, supp. xxxvii, 339.
39. BEEUWKES, H.: De Reactie van Paul en Bunnell, *Nederl. tijdschr. v. geneesk.*, 1939, lxxxiii, 149.
40. SMEALL, J. T.: Glandular fever (infectious mononucleosis), *Edinburgh Med. Jr.*, 1942, xlix, 291.

41. KAUFMAN, R. E.: False positive serologic reactions for syphilis in infectious mononucleosis, *Jr. Lab. and Clin. Med.*, 1941, xxvi, 1439.
42. GOUNELLE, H., and FOLLIN, S.: Mononuclease infectieuse avec rechute et syndrome digestif, *Sang*, 1939, xiii, 676.
43. DOWNEY, H., STASNEY, J., and MCKINLAY, C. A.: Infectious mononucleosis, *Jr. Am. Med. Assoc.*, 1935, cv, 761. Discussion by Dr. I. Davidsohn.
44. ERF, L. A.: Acute infectious mononucleosis with unidentified structures in the supravital preparations of the lymph nodes, *Jr. Mt. Sinai Hosp.*, 1936, iii, 113.
45. ROSENTHAL, N., and WENKEBACH, G.: Die Bedeutung der heterophilen Antikörperreaktion für die Diagnose der infektiösen Mononuclease, *Klin. Wchnschr.*, 1933, xii, 499.
46. NOLAN, R. A.: Report of a so-called epidemic of glandular fever (infectious mononucleosis), *U. S. Naval Med. Bull.*, 1935, xxxiii, 479.
47. BANG, O., and KRISTENSEN, M.: Kliniske Undersogelser over Forekomsten af Faareblodlegeme-Agglutinin (Heterofilt Antistof), *Ugesk. f. laeger*, 1936, xcvi, 1049.
48. DAVIDSOHN, I.: Personal communication.
49. SOHIER, R., PARNET, J., and BERNIER, G.: Diagnostic serologique de la mononucléose infectieuse par le test d'agglutination (réaction de Paul-Bunnell). Sa valeur pratique, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1939, lv, 846.
50. WERLIN, S. J., DOLGOPOL, V. B., and STERN, M. E.: Infectious mononucleosis—a diagnostic problem, *Am. Jr. Med. Sci.*, 1941, cci, 474.
51. STRAUS, R., and BERNSTEIN, M. T.: Further serological studies in infectious mononucleosis, *Am. Jr. Clin. Path.*, 1942, xii, 174.
52. CANZANI, R.: La suerologia de la febre ganglionar o mononucleosis infecciosa, *Arch. urug. de med., cir. y especialid.*, 1942, xx, 104.
53. JOHANN, A.: Zur Frage der diagnostischen Verwertbarkeit der Hanganutziu-Deicherschen Reaktion beim Pfeifferschen Drüsenfieber, *Ztschr. f. Immunitätsf. u. exper. Therap.*, 1941, c, 292.
54. MCALPIN, K.: Infectious mononucleosis, report of a case with 42,000 leucocytes, *New York State Jr. Med.*, 1936, xxxvi, 908.
55. WORMS, R., and DEMANCHE, R.: A propos de la réaction de Paul et Bunnell dans la mononucléose infectieuse. Sa date d'apparition, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1939, lv, 1215.
56. HIMSWORTH, H. P.: Infective mononucleosis and the Paul-Bunnell test, *Lancet*, 1940, i, 1082.
57. DEMANCHE, R.: Evolution des réactions sérologiques au cours de la mononucléose infectieuse, *Sang*, 1939, xiii, 680.
58. DEMANCHE, R.: Le séro-diagnostic de la mononucléose infectieuse, *Sang*, 1938, xii, 86.
59. DEMANCHE, R.: Le diagnostic de la mononucléose infectieuse: Valeur des réactions sérologiques, *Presse méd.*, 1939, xlvii, 1614.
60. DURUPT, A.: Le diagnostic sérologique des mononucléoses infectieuses, *Presse méd.*, 1937, xlv, 1218.
61. LYGH, C. E.: Infectious mononucleosis, *Jr. Lancet*, 1938, lviii, 91.
62. KENT, C. F.: "False" positive Paul-Bunnell (heterophile) reaction? *Am. Jr. Clin. Path.*, 1940, x, 576.



## "ATYPICAL" CORONARY DISEASE IN YOUNG PEOPLE \*

By JOSEPH WEINSTEIN, MAJOR, MC, F.A.C.P., *Brooklyn, N. Y.*

THE title "Atypical Coronary Disease" was selected advisedly, since the term coronary disease has long been used synonymously with coronary sclerosis (atheromatous). In this sense, disease of the coronary arteries on any other basis would be atypical.

Our interest in atypical changes in the vascular system as affecting the coronary vessels was stimulated by a series of 10 cases observed at the Station Hospital, Fort Ord, California over a three month period.

None of the patients died, so that in the absence of autopsy investigations, one can, at best, only postulate as to the pathology or its etiologic basis.

### CASE REPORTS

*Case 1.* W. H. H. The patient was a 20 year old colored soldier who had been a blacksmith in civilian life and who had been in military service four months. His family history was not contributory. He had suffered severe sore throats as a child. There was nothing else pertinent in his past history. He denied any venereal history. He never smoked. He was admitted to the hospital on December 1, 1942, with the story that for the past five years he had been suffering attacks of precordial pain which had become worse in the past three months. The pain radiated to the left shoulder and down the left upper extremity and stopped either at the elbow or went down to the finger tips. The attacks usually came on with exertion or excitement and occasionally at rest. About three weeks before admission, he suffered an upper respiratory infection. On the day before admission he had a very severe precordial pain which lasted about an hour and left him weak and perspiring.

Physical examination was entirely negative except for a slight enlargement of the heart to the left and a transient soft apical systolic murmur. His blood pressure was 125 mm. Hg systolic and 80 mm. diastolic and remained at that level. There was no temperature elevation and no increase in the pulse or respiratory rate. The leukocyte and differential count remained normal, but the red cell sedimentation rate was very rapid and remained rapid for about eight weeks. The basal metabolic rate was  $\pm 0$ ; blood Kahn and Wassermann reactions were negative; blood sugar, 83 mg. per 100 c.c. of serum; blood cholesterol, 215 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 250 units. Electrocardiograms (figure 1) taken 48 hours after onset showed a depressed  $RT_2$  and an inverted  $T_1$ ,  $T_2$  and  $T_3$ . Tracings taken 10 days after onset showed the  $RT_2$  more depressed but a diphasic  $T_1$ . Tracings taken six weeks after onset show no  $RT$  depression,  $T_1$  positive but depressed, and  $T_2$  and  $T_3$  inverted but less marked in degree. No QRS changes were observed at any time. The clinical course was uneventful.

*Case 2.* L. C. Patient was a 20 year old colored soldier who had been in military service 15 months. His family history was not contributory. He had

\* Read in part before the 72nd Annual Session of the California Medical Association, May 1943.

Received for publication August 11, 1943.

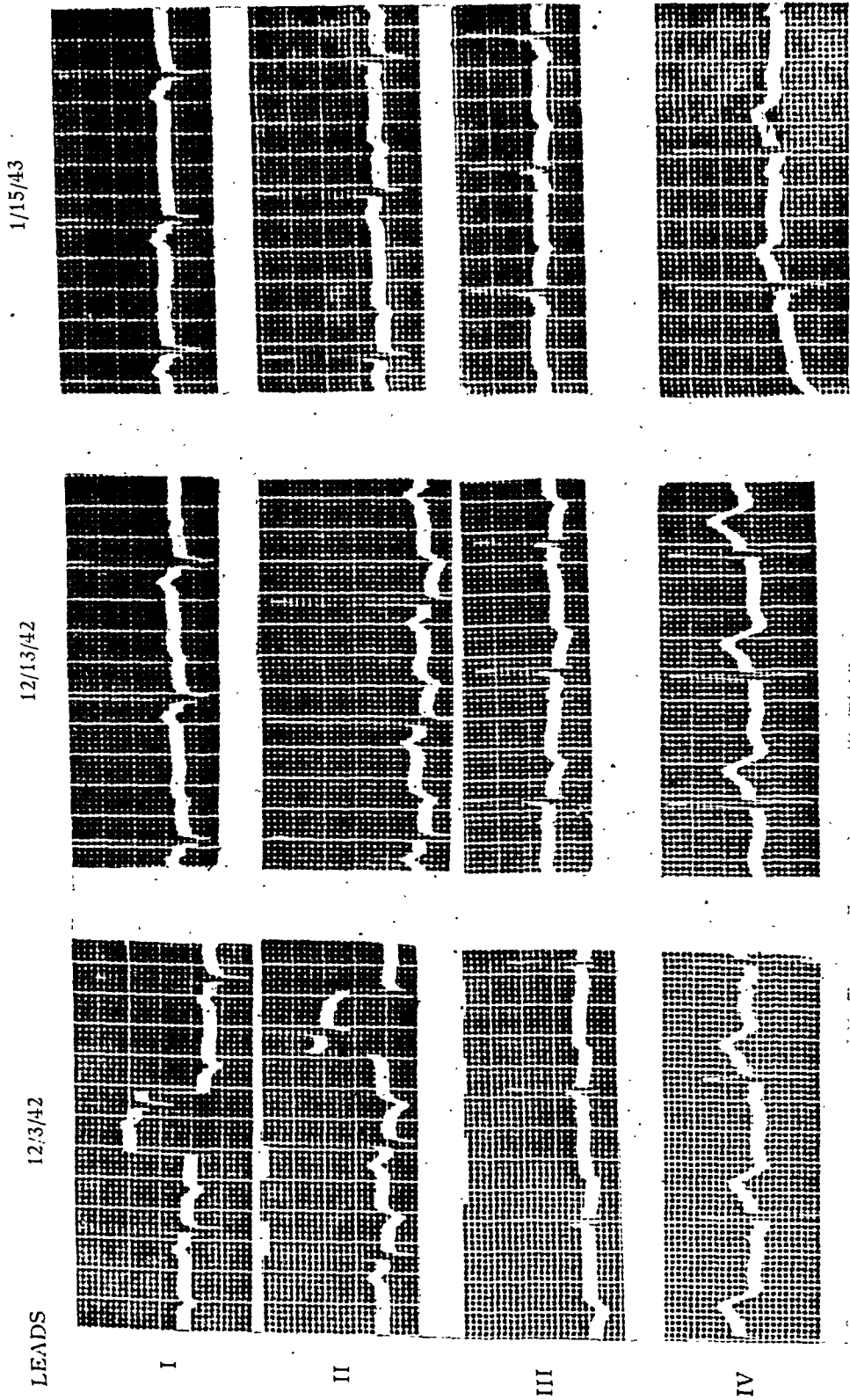


Fig. 1: Case 1.

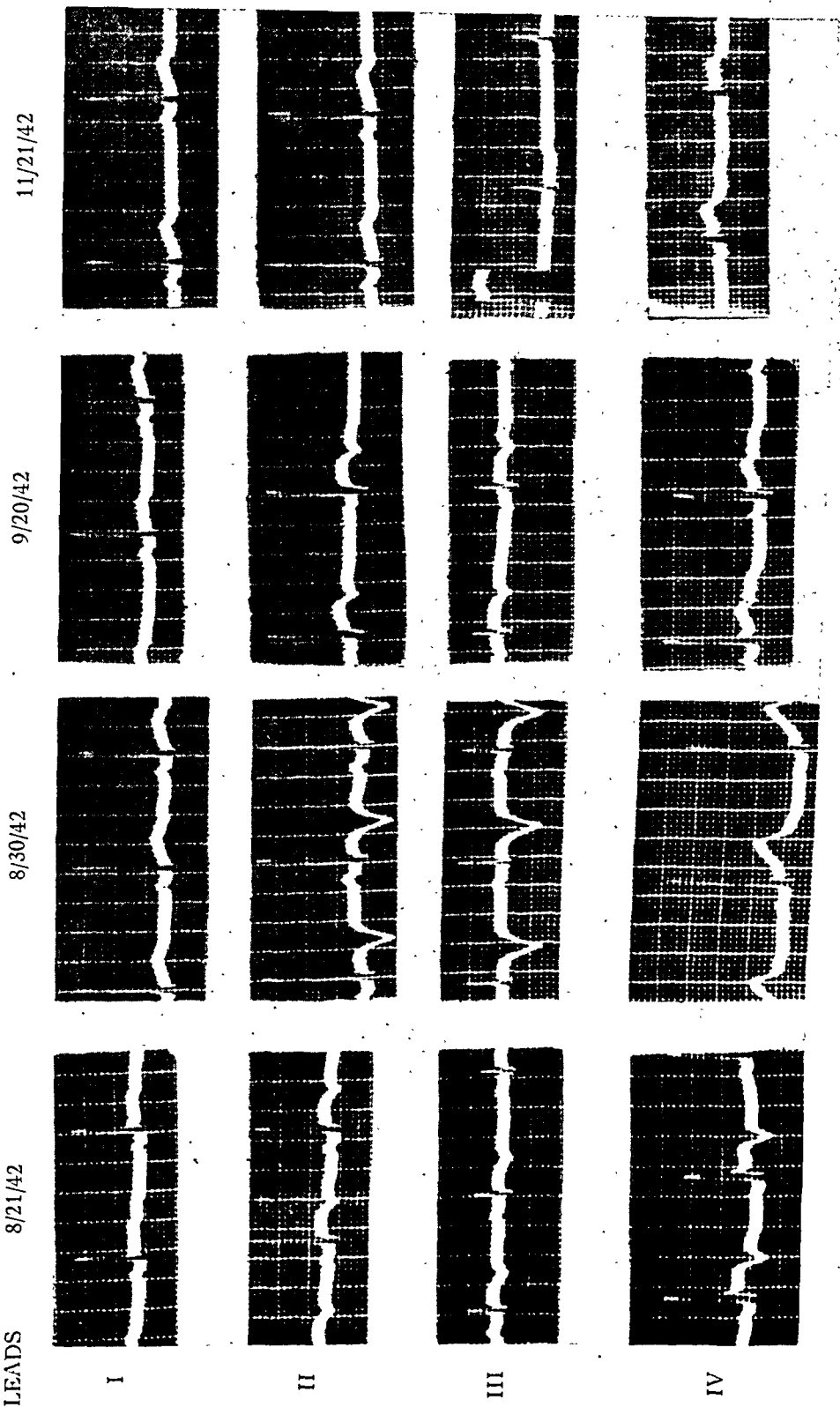


Fig. 2. Case 2.

suffered frequent sore throats as a child, and there was nothing else pertinent in his past history. He denied any venereal history. He was a moderate smoker. He was admitted to the hospital on August 19, 1942, with the story that four days before admission he developed a severe sore throat. He remained on duty, but on the third day he developed substernal pain. It was very severe for one day and persisted for about three days.

Physical examination was entirely negative except for inflamed tonsils and pharynx. The heart was not enlarged, sounds were of good quality, and no murmurs or friction râles were heard. His blood pressure was 122 mm. Hg systolic and 80 mm. diastolic on admission and remained at that level. The temperature was elevated on admission but was otherwise normal throughout the period of his hospital observation. There was no increase in his pulse or respiratory rate. Roentgenographic and fluoroscopic examinations of his heart were normal at all times. There was no leukocytosis, and the differential count remained normal. The red cell sedimentation rate was very rapid and remained rapid for four and one-half weeks. His basal metabolic rate was plus 2; blood Kahn and Wassermann reactions were negative; blood sugar 86 mg. per 100 c.c. of serum; blood cholesterol 194 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 250 units. Electrocardiograms (figure 2) taken 24 hours after onset of the substernal pain showed a slight RT elevation in Leads I and II and a marked  $RT_4$  elevation and inverted  $T_2$ ,  $T_3$  and  $T_4$ . At the end of the third week the tracings showed a marked T inversion in Leads II and III with the picture of a characteristic posterior wall infarction. At the end of four months the pattern of all leads was approaching normal. There were no QRS changes at any time. The clinical course was uneventful.

*Case 3.* B. P. Patient was a 21 year old colored soldier, a farmer in civilian life, who had been in military service about two months. His family history was not contributory. He had suffered severe sore throats as a child, and for 13 years he was troubled with a chronic arthritic condition of the hands. There was nothing else pertinent in his past history. He denied any venereal infection. He never smoked. He was admitted to the hospital on November 5, 1942 with the story that for three weeks prior to admission he had suffered with severe sore throats. After admission to the hospital, he developed pains in his left hand, wrist and elbow, and he started complaining of precordial distress with exertion.

The only pertinent findings on physical examination were enlarged and inflamed tonsils and mild contractures of both hands. The heart was not enlarged and no pertinent adventitious sounds were heard. His blood pressure was 118 mm. Hg systolic and 70 mm. diastolic and remained at that level throughout his hospital stay. There was no temperature elevation and no increase in the pulse or respiration rate. There was no leukocytosis and his differential count remained normal. His red cell sedimentation rate was elevated for about 10 days. His basal metabolic rate was plus 4; blood Kahn and Wassermann reactions were negative; blood sugar 106 mg. per 100 c.c. of serum; blood cholesterol 215 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 350 units. Electrocardiograms (figure 3) taken three days after the onset of the precordial pain showed an inversion of  $T_2$  and a diphasic  $T_3$  with no RT changes. Serial studies over a period of three months showed a gradual return toward the normal pattern. There were no QRS changes at any time. The clinical course was uneventful. The contractures of both hands have persisted unchanged.

*Case 4.* J. A. L. Patient was a 25 year old white soldier, a hospital attendant as a civilian, who had been in military service 20 months. His family history was not contributory. He had suffered frequent sore throats as a child. There was noth-

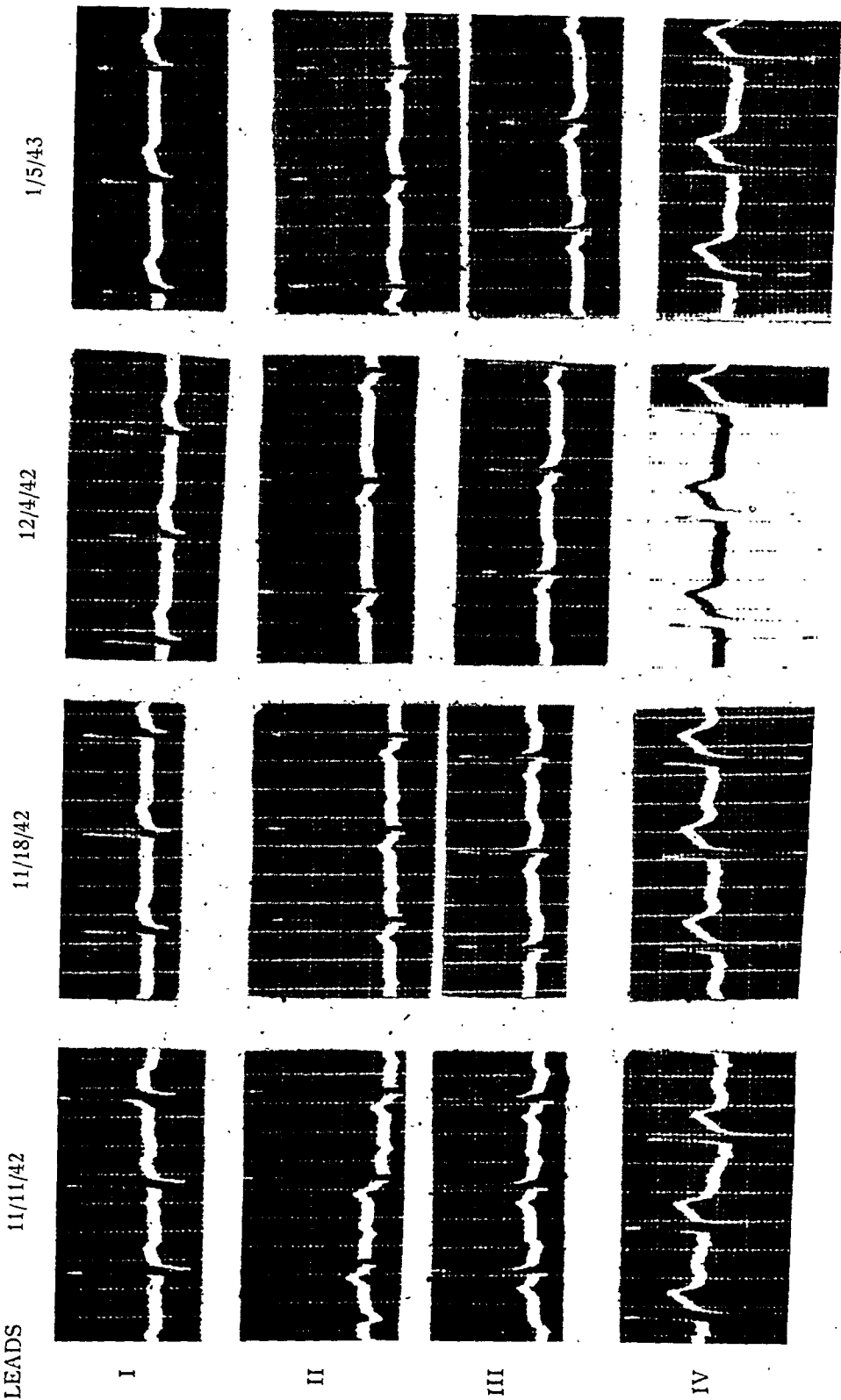


FIG. 3. Case 3.

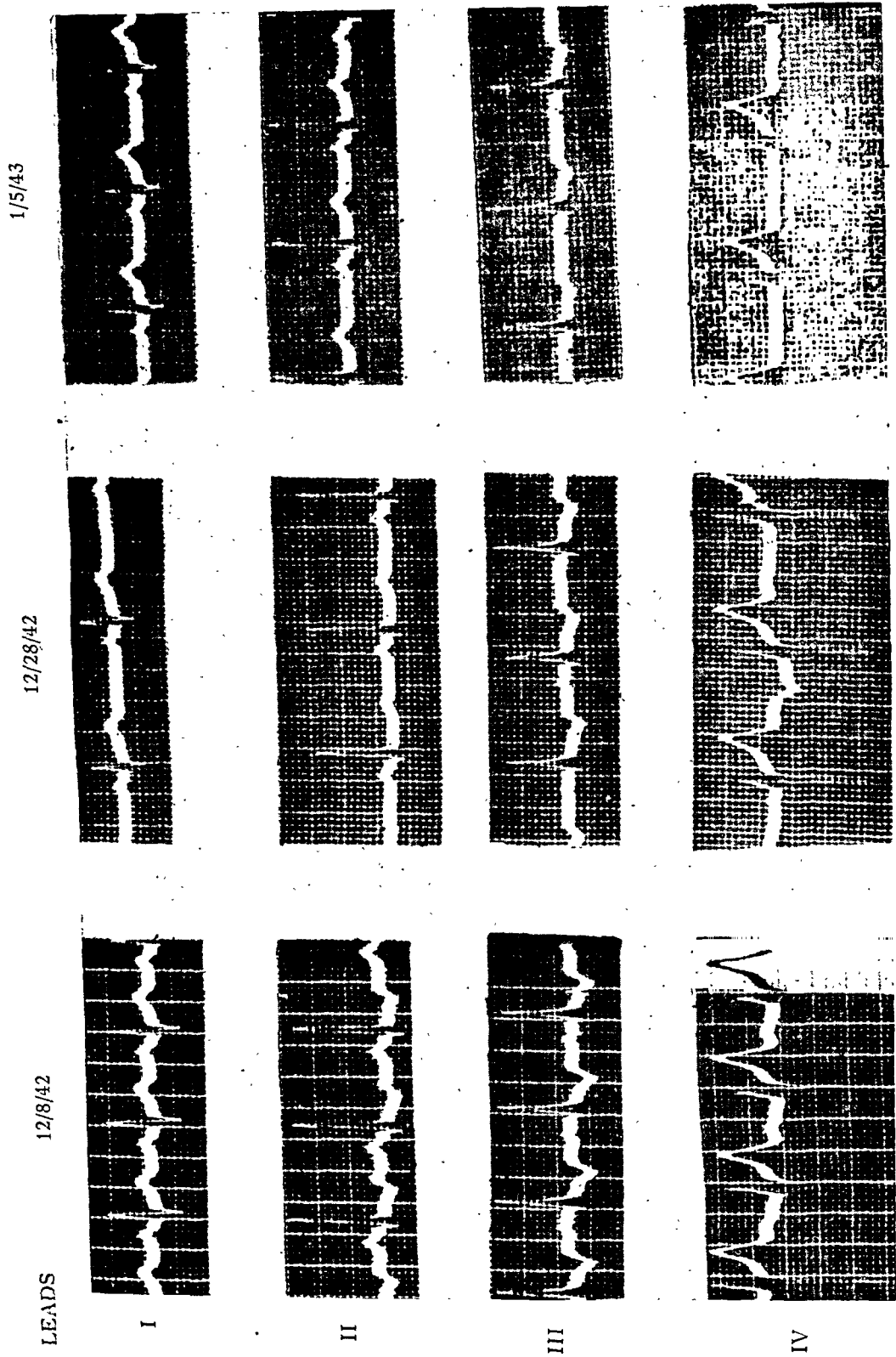


FIG. 4. Case 4.

ing else pertinent in his past history. He denied any venereal infection. He was a heavy smoker. He had had an upper respiratory infection about two weeks before admission but continued at his work. On the night before admission, while doing routine ward duties, he experienced sudden sharp substernal pain which radiated down both arms. The pain lasted about 30 minutes and left him weak and perspiring profusely.

On physical examination his tonsils appeared chronically diseased, scarred, pitted and ragged. The examination was otherwise negative. His heart was not enlarged, and no adventitious sounds were heard. His blood pressure was 122 mm. Hg systolic and 60 mm. diastolic on admission and remained within that range through his hospital stay. There was no temperature elevation and no increase in his pulse or respiratory rate. There was no leukocytosis and his differential count remained normal. His red cell sedimentation rate was elevated and remained elevated for about four weeks. His basal metabolic rate was plus 4; blood Kahn and Wassermann reactions were negative; blood sugar was 80 mg. per 100 c.c. of serum; blood cholesterol 225 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. Electrocardiograms (figure 4) taken 24 hours after the attack showed an inverted  $T_2$  and  $T_3$  with no appreciable RT change. Serial studies showed a gradual return of the abnormal variations to normal. No QRS changes were observed at any time. The clinical course was uneventful. There was no recurrence of the pain.

*Case 5.* J. O. T. Patient was a 27 year old white officer, a lumber dealer in civilian life, who had been in military service six months. His family history was not contributory. He had suffered severe sore throats, necessitating a tonsillectomy, as a child. There was nothing else pertinent in his past history. He denied any venereal infection. He was a moderate smoker. He was admitted to the hospital on December 4, 1942, with a story that about four weeks before admission he had suffered with severe sore throats for a period of four days. Two weeks later he developed generalized stiff painful joints, which lasted for several days. Twenty-four hours before admission he developed severe vice-like pains over the precordium. The pain radiated to the elbows of both arms and was more marked on the left side. The pain would last for several hours at a time. He required repeated hypodermic injections of morphine to control the pain.

Physical examination revealed a pharyngitis. There was a transient soft localized apical systolic murmur. His heart was not enlarged. His blood pressure was 110 mm. Hg systolic and 80 mm. diastolic on admission and dropped to 90 mm. systolic and 70 mm. diastolic two days later. He ran a temperature of about 100.5° F. for about three days. He had a moderate tachycardia during this period. There was no cyanosis or dyspnea. There was no leukocytosis and his differential count remained normal. His red cell sedimentation rate was very rapid and remained rapid for about five weeks. His blood Kahn reaction was negative; blood sugar 80 mg. per 100 c.c. of serum; blood cholesterol 160 mg. An antistreptolysin titer determination showed 833 units. Electrocardiograms (figure 5) taken 24 hours after onset showed only an  $RT_2$  elevation. On serial studies, T inversions developed characteristics of an anterior wall infarction. No QRS changes were observed. Tracings taken about two months after the onset showed a tendency of the pattern of all leads to revert back to normal. The clinical course was uneventful. There was no recurrence of the pain.

*Case 6.* P. W. B. Patient was a 28 year old colored soldier, a farmer in civilian life, who had been in military service four months. Two of his sisters had rheumatic heart disease. He gave a story of having had a rheumatic infection at the age of 10. He also suffered throat infections as a child. He had had an uncomplicated gonorrhea at the age of 15, which was treated and pronounced cured. He never smoked.

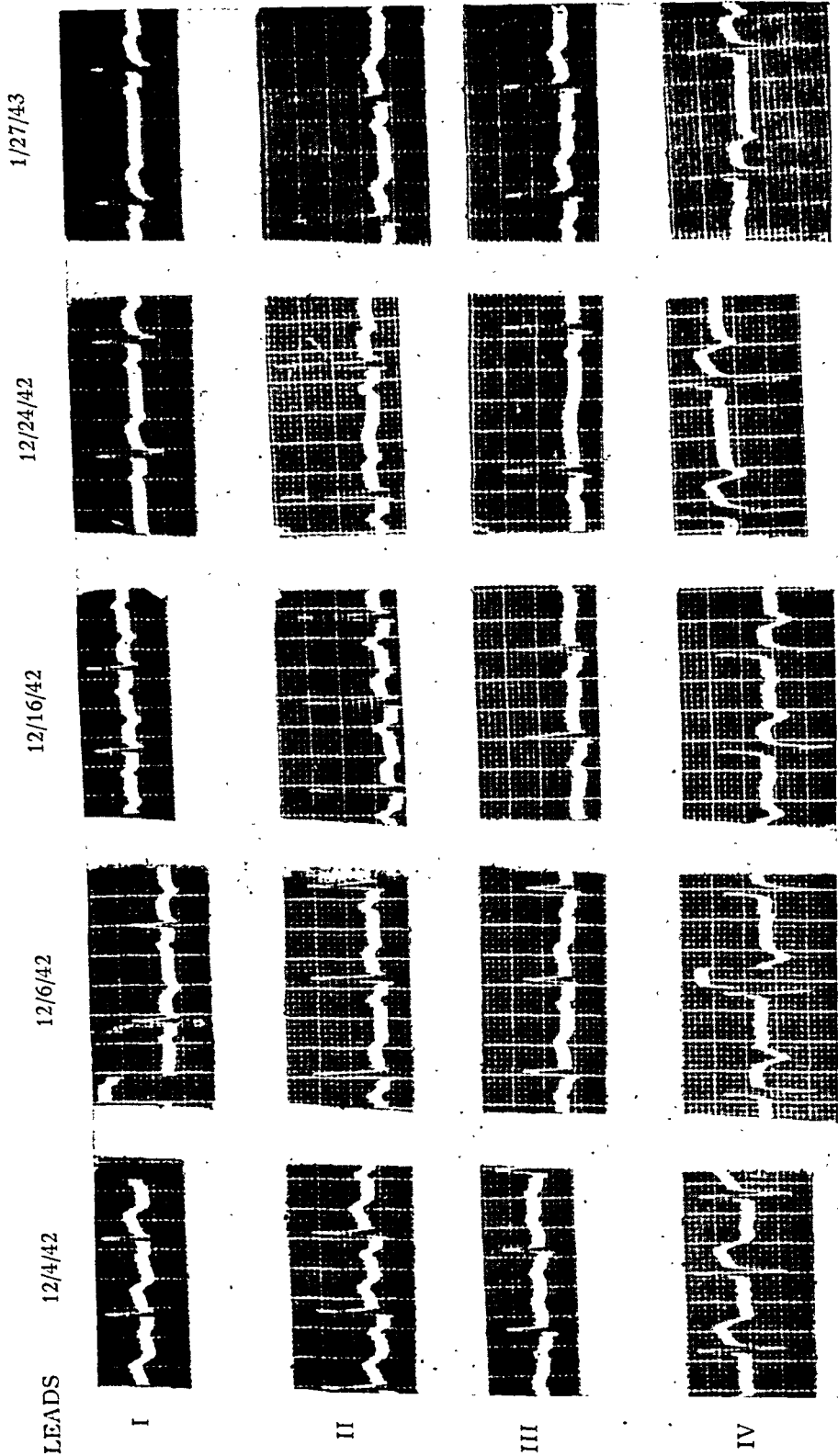


FIG. 5. Case 5.



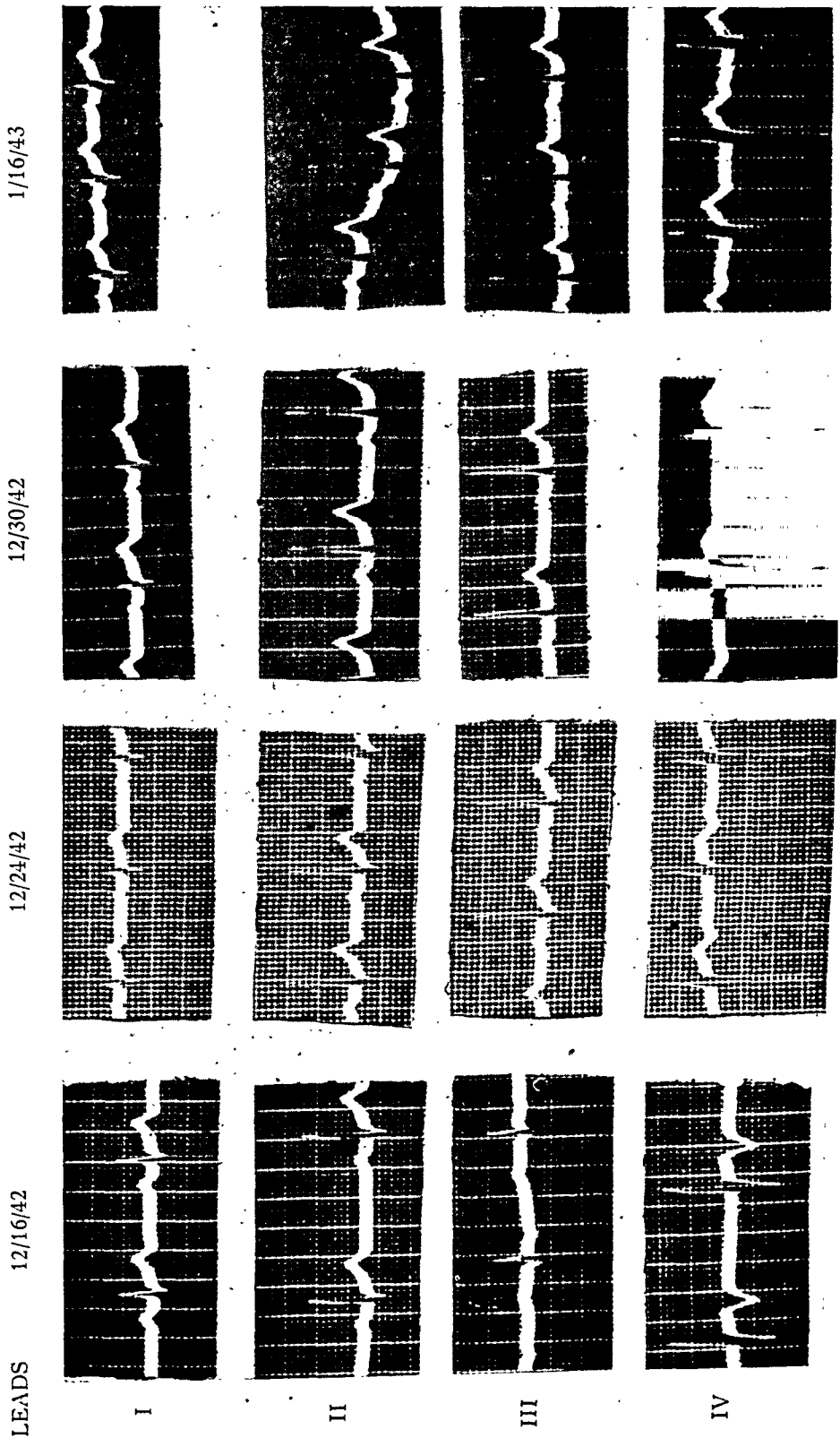


Fig. 6. Case 6.

For a period of about five years prior to his admission to the hospital, he had been suffering attacks of precordial pain. The pain radiated to the left shoulder, down the inner side of the left arm to the fingers. Attacks occurred with exertion and subsided with rest. About 10 days before admission he had an upper respiratory infection which lasted a few days. On the day before admission he had an attack of pain which lasted about 15 minutes and left him weak and perspiring.

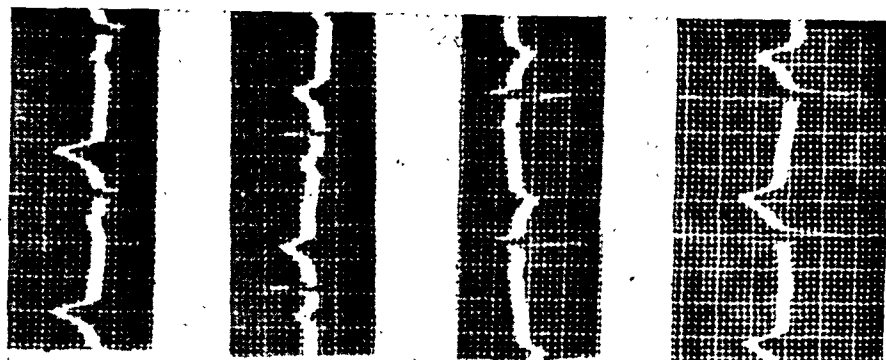
Physical examination was entirely negative except for a moderate pharyngitis. The heart was not enlarged, and there were no abnormal sounds. His blood pressure was 150 mm. Hg systolic and 90 mm. diastolic on admission and ranged around 135 mm. systolic and 80 mm. diastolic during his hospital stay. There was no temperature elevation. There was no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was moderately elevated for about two weeks. His basal metabolic rate was minus 2; blood Kahn and Wassermann reactions were negative; blood sugar was 96 mg. per 100 c.c. of serum; and blood cholesterol 166 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 200 units. Electrocardiograms (figure 6) taken 48 hours after onset showed an inverted  $T_4$  with no appreciable RT change. Serial studies showed the  $T_4$  becoming diphasic and finally upright with a normal pattern. No QRS changes were observed at any time. He continued to have occasional mild anginal manifestations on effort. These were relieved by rest and also by nitroglycerine, 1/200 grain under the tongue. The clinical course was otherwise uneventful.

*Case 7. D. S.* The patient was a 33 year old white male, a truck driver in civilian life, who had been in military service three months. His family history was not contributory. He had had a tonsillectomy at the age of 21 because of severe sore throats. There was nothing else pertinent in his past history. He denied any venereal infection. He was a heavy smoker. He was admitted to the hospital on November 4, 1942, with a story that several weeks before admission he suffered a throat infection. For a week prior to admission, he noticed progressive dyspnea and gagging when hiking. The night before admission, while sitting quietly, he suddenly developed severe pain over the precordium. He vomited and collapsed. The pain lasted about half an hour.

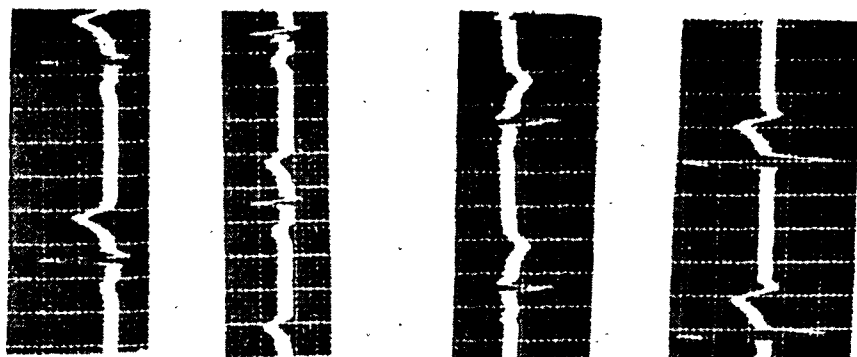
Physical examination was entirely negative except for infected tonsillar tabs. The heart was not enlarged, and there were no adventitious sounds. His blood pressure was 120 mm. Hg systolic and 80 mm. diastolic on admission and remained within normal range. There was no temperature elevation and no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was markedly elevated and remained elevated for about six weeks. His basal metabolic rate was plus 3; blood Kahn and Wassermann reactions were negative; blood sugar was 95 mg. per 100 c.c. of serum; and blood cholesterol, 195 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 350 units. Electrocardiograms (figure 7) taken 24 hours after admission showed a slight RT elevation and a deeply inverted  $T_4$ . On serial study, there was a gradual return to normal in about eight weeks. No QRS changes were observed at any time. The clinical course was uneventful.

*Case 8. E. K.* The patient was a 36 year old colored soldier, a laborer in civilian life, who had been in military service four months. His family history was not contributory. He had had frequent sore throats as a child. There was nothing else pertinent in his past history. He denied any venereal infection. He was a light smoker. He was admitted to the hospital on December 7, 1942 with a story that he had been suffering with severe sore throats and hoarseness for a month. After his admission to the hospital, he developed joint disturbances, involving his left

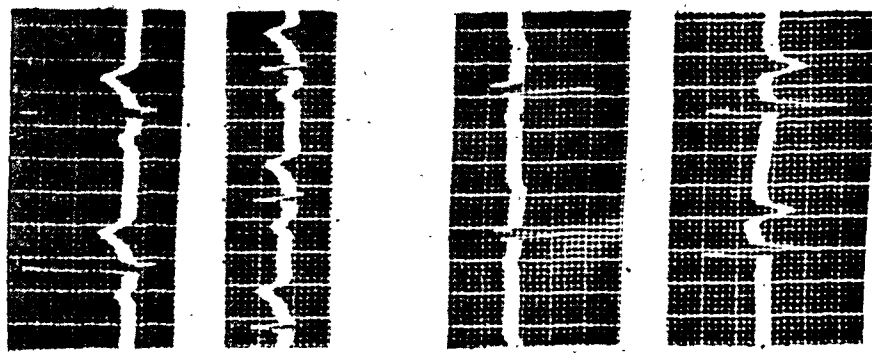
1/5/43



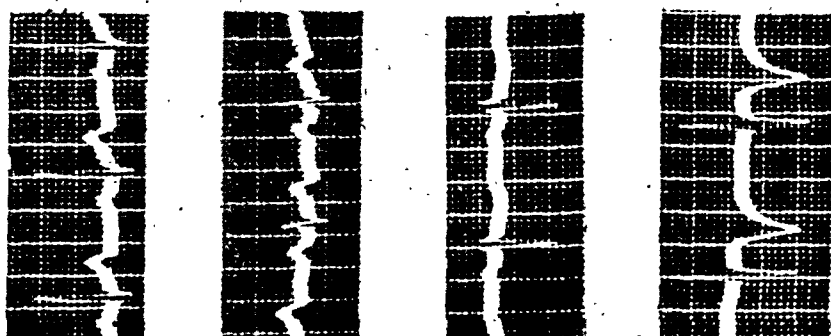
11/30/42



11/16/42



11/6/42



LEADS

I

II

III

IV

FIG. 7. Case 7.

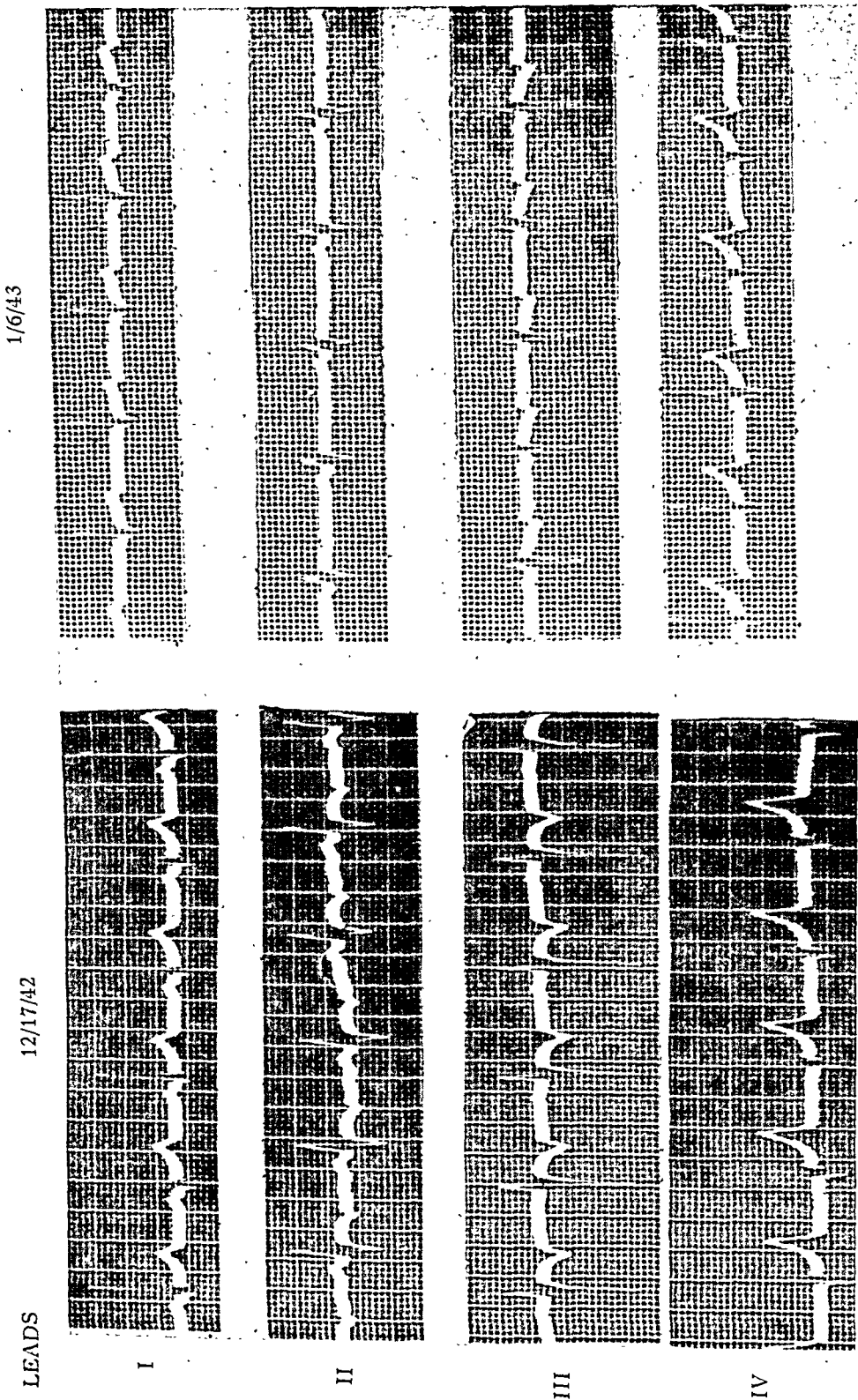


Fig. 8. Case 8.

shoulder and left knee. He also developed a precordial discomfort aggravated by exertion.

On physical examination, there was a pharyngitis. The heart was not enlarged, and no adventitious sounds were heard. The left knee and shoulder were painful on motion with no abnormal physical findings. His blood pressure was 112 mm. Hg systolic and 78 mm. diastolic on admission and remained at about that level during his hospital stay. There was no temperature elevation and no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was elevated for about 10 days. His basal metabolic rate was plus 6; blood Kahn and Wassermann reactions were negative; blood sugar was 83 mg. per 100 c.c. of serum; blood cholesterol 192 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 180 units. Electrocardiograms (figure 8) taken about 72 hours after the onset of precordial pain showed a slight coving and inversion of  $T_2$  and an inverted  $T_3$ . On serial study at the end of about 10 weeks, there was a tendency for a return to a normal pattern. There was a left axis deviation but no pertinent QRS changes at any time. The clinical course was uneventful.

*Case 9.* J. L. W. The patient was a 37 year old colored soldier, a laborer in civilian life, who had been in military service three months. His family history was not contributory. He had suffered frequent sore throats as a child, and he had had pneumonia at the age of 33. He denied any venereal infection. He was a moderate smoker. He was admitted to the hospital on October 30, 1942, with a story that for many years he had been suffering from a localized precordial pain. It came on with exertion, was not sufficient to stop him but would slow him down. About two weeks before admission he suffered a throat infection for about four days. Three days before admission, while getting out of bed in the morning, he developed a severe, localized compressing precordial pain, which lasted several days.

Physical examination was entirely negative except for bilateral hypertrophied inflamed tonsils. The heart was not enlarged, and no adventitious sounds were heard. His blood pressure was 134 mm. Hg systolic and 82 mm. diastolic and remained at about that level. There was no temperature elevation and no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was elevated for about three weeks. His basal metabolic rate was minus 3; blood Kahn and Wassermann reactions were negative; blood sugar was 83 mg. per 100 c.c. of serum; and blood cholesterol 200 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 166 units. Electrocardiograms (figure 9) taken four days after the onset of the attack showed an inverted  $T_2$  and  $T_3$  of low voltage and diphasic  $T_4$ . There were no appreciable RT changes. Serial studies showed a gradual return to normal pattern in about six weeks. There were no QRS changes at any time. The clinical course was uneventful.

*Case 10.* H. P. L. The patient was a 37 year old white soldier, a farmer in civilian life, who had been in military service three months. His family history was not contributory. There was nothing pertinent in his past history aside from sore throats as a child. He denied any venereal infection. He was a mild smoker. He was admitted to the hospital on November 24, 1942, because of a severe reaction to typhoid inoculation. On routine questioning he gave a story that about one year before admission to this hospital he developed a polyarthritides of fleeting character and fever. Three days later badly infected tonsils were removed. Ten days after the tonsillectomy, he suffered an attack of severe substernal pain. The pain radiated to the left shoulder and arm. He was confined to a hospital for about four months. The diagnosis of an acute coronary occlusion was made and confirmed by electrocardio-

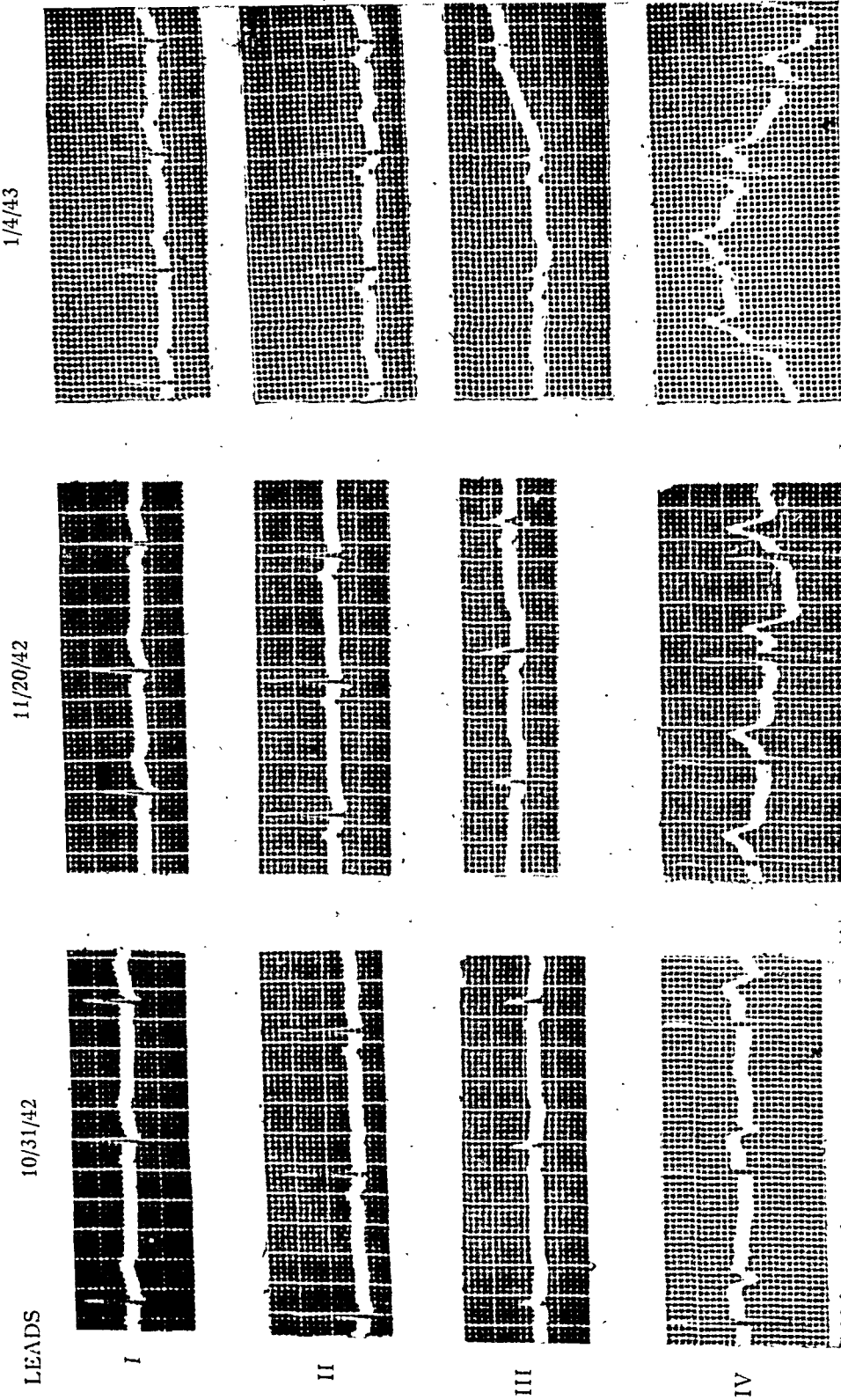


FIG. 9. Case 9.

graphic examination. He had a slight elevation of temperature of about 100.5° F. for several days. There was no leukocytosis, but a rapid red cell sedimentation rate. After a prolonged convalescence, he returned to farming until his induction into military service. At this time he had no symptoms referable to his cardiovascular system.

Physical examination at the time of the present hospital admission was entirely negative. The heart was not enlarged and responded normally to exercise. Chest roentgenogram was normal; blood count and red cell sedimentation rate were normal; urinalysis was normal. His basal metabolic rate was plus 4. Blood Kahn and Wassermann reactions were negative. Blood sugar was 104 mg. per 100 c.c. of serum; blood cholesterol 190 mg. Tuberculin test was negative. Electrocardiograms (figure 10) taken four days after the attack of the previous year showed a slight  $RT_2$  and  $RT_3$  depression and an inverted  $T_2$  and  $T_3$ . Tracings taken almost one year later were entirely normal.

LEADS

11/3/41

11/30/42

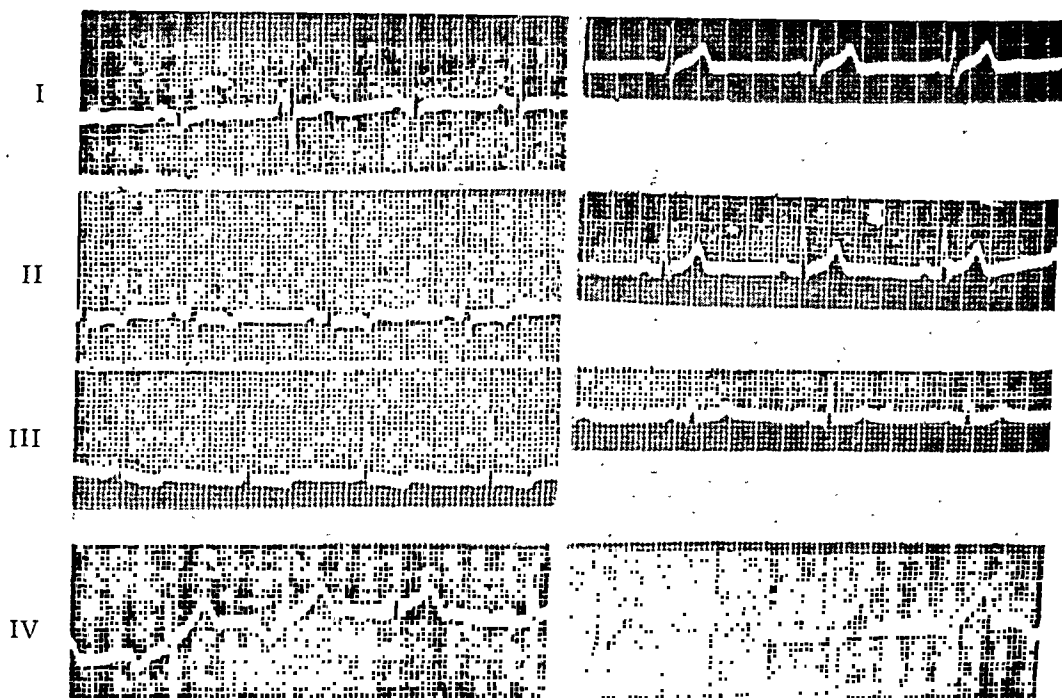


FIG. 10. Case 10.

*Analysis of the Case Reports* (table 1). It is observed that the ages of the patients ranged between 20 and 37. Six of the 10 were under 30, and the average age of the entire group was 28.4 years. Six of the 10 cases were negroes.

The family history was not contributory except in case 6, where two sisters are supposed to have had rheumatic fever. The patient gave a story that he, too, had rheumatic fever at the age of 10, although no evidence of valvular heart disease was evident during the period that we observed him. All the cases gave histories of severe throat infections during childhood.

CHART I

Electrocardiograms																									
Physical and Laboratory Findings												History of Attack				Past History		Race				F.H.			
No.	Age	Race	F.H.	T.I.		A.P.	To- bacco	U.R.I.				Card. Pain	Col- lapse	U.R.I.	Card. Find.	Fever	Leuk.	Rapid S. Rate	Bl. Chol.	Anti- strepto- lysin Titer	QRS Ch.	RT Ch.	T Changes		EKG Rec.
				Ant.	W. Post																				
1	20	Col.	N.C.	x		x	0			Slt. E. TSM		0	x	215	250 U	0	x						x		x
2	20	Col.	N.C.	x		xxx	xxx					0	x	194	250 U	0	x						x		x
3	21	Col.	N.C.	x		xx	0					0	x	215	350 U	0							x		
4	25	Wht.	N.C.	x		xxx	xxx					0	x	225		0							x		x
5	27	Wht.	N.C.	x		xx	xx			TSM	100.5 3 da	0	x	160	833 U	0	x								
6	28	Col.	R.F.	x		x	0					0	x	153	200 U	0							x		x
7	33	Wht.	N.C.	x		xxx	xxx					0	x	195	350 U	0	x						x		x
8	36	Col.	N.C.	x			x					0	x	192	180 U	0									x
9	37	Col.	N.C.	x		x	xx					0	x	200	166 U	0							x		x
10	37	Wht.	N.C.	x			x				100.5 4 da	0	x	190		0							x		x

Tuberculin tests, tests for brucellosis, and coccidioidomycosis were negative in all cases. Blood sugar determinations were normal in all cases. Basal metabolic rates were within normal range in all cases. Blood Kahn and Wassermann reactions were negative in all cases.

N.C.—Not Contributory  
R.F.—Rheumatic Fever  
T.I.—Throat Infections  
T.S.M.—Transient Systolic Murmur

A.P.—Angina Pectoris  
U.R.I.—Upper Respiratory Infections  
J.P.—Joint Pains



Three of the cases were heavy smokers, two more moderate smokers, two mild smokers and three cases did not smoke at all. No relationship of the use of tobacco to the disease can be drawn from these figures.

In all of the cases a respiratory infection preceded the cardiac attack by a period of several days to four weeks. In four of the cases there were associated joint disturbances.

The attacks were characterized by only moderate precordial pain in four of the 10 cases. The remaining six cases were characterized by severe precordial pain, and in four of these there was associated collapse. Three of the 10 cases, including case 1, age 20, gave a story of having suffered an angina of effort dating back five years or more, which would mean that case 1 started complaining of angina pectoris at the age of 15.

On physical examination, nine of the 10 cases had evidence of throat inflammation. Cardiac findings were negligible. Only case 1 showed evidence of slight enlargement of the heart to the left, both on physical examination and by chest roentgenogram. Two of the cases had transient apical systolic murmurs. Cases 5 and 10 had a low grade fever and a moderate tachycardia for three or four days at the onset.

There was no leukocytosis in any case, but all had rapid red cell sedimentation rate determinations. Blood cholesterol figures were within normal limits or only slightly elevated. Blood sugars were normal, basal metabolic rates were within normal limits. Tuberculin tests and tests for brucellosis and coccidioidomycosis were negative in all cases. Blood Kahn and Wassermann reactions were negative in all cases.

Antistreptolysin titers were obtained in eight of the 10 cases. In five, the figures were high enough to implicate the hemolytic streptococcus. There is a question as to how much reliance can be placed on the significance of the negative results in the remaining three cases, since the titer determinations were made two to three months after the acute respiratory episode had subsided in these cases.

An analysis of the electrocardiographic variations shows that there were no appreciable QRS changes in any case. Four cases showed RT changes; but all showed T changes, which indicated posterior wall localization in six cases and anterior wall localization in four. In six of the 10 cases the electrocardiographic patterns reverted to normal. In three of the cases there was a partial return. Only in case 1 did the changes appear to be permanent. This was the 20 year old patient who had suffered angina pectoris since the age of 15.

#### DISCUSSION

In all the cases, the clinical picture, course and electrocardiographic variations were suggestive of an unusual type of cardiac infarction. Most authors are in general agreement that cardiac infarction, secondary to a coronary occlusion on a coronary sclerotic basis, occurs most commonly over the age of 40, infrequently between the ages of 30 and 40, and very rarely under 30. Levine<sup>1</sup> reports only three instances between the ages of 30 and 39 in a total of 145 consecutive cases. There is also general agreement that

the occurrence is relatively uncommon in the negro as compared to the white race. In this series of cases, 60 per cent are between the ages of 20 and 28 and 60 per cent are in negroes. The ratio of negro to white troops at this camp during this period was comparatively small.

The high incidence of throat infections in the past history, the common onset of the cardiac manifestations following respiratory infections, usually sore throats, and in four instances the presence in addition of joint disturbances are highly suggestive of an infectious basis for the disease picture.

Three of the cases with the same history of throat infections, similar clinical picture, course and characteristic electrocardiographic variations had, in addition, a long history of angina, typically vascular in type. These three cases seem to fall into a separate group under the same heading. Associating the two groups it is logical to assume a vascular basis for the disease. In both groups we can assume recent vascular lesions and in the second group, in addition, preëxisting vascular changes.

It is widely accepted that rheumatic fever is closely associated with hemolytic streptococcus infections. Five of the eight cases of our series, on whom antistreptolysin titers were determined, showed figures high enough to be significant, with a plausible reason as to why they were not high in the remaining three. Coburn<sup>2</sup> found that the titer, as a rule, remains high as long as the disease remains active.

Jones and Mote<sup>3</sup> found that 58 per cent of the initial rheumatic attacks were preceded by infections of the upper respiratory tract, and that in 271 observed recurrent attacks, 67 per cent were associated with infections of the respiratory tract, two-thirds of which were manifested by sore throat.

Arterial changes occurring in rheumatic fever were discussed by French authors as far back as 1870 (Hayem,<sup>4</sup> Martin,<sup>5</sup> Landouzy and Siredey,<sup>6,7</sup> and Huguenin<sup>8</sup>). Von Glahn and Pappenheimer<sup>9</sup> in 1926 accurately described the peripheral vascular changes according to our present conception, and Karsner and Bayless<sup>10</sup> thoroughly studied lesions of the coronary arteries in rheumatic infections. They speak of inflammatory and fibrotic lesions of the coronary arteries and mention that fibrinoid degeneration with the formation of a fibrin-like material is particularly suggestive but not diagnostic. Boyd<sup>11</sup> writing on this point remarks "the most important lesion is an intimal fibrosis of the coronary vessels in early life thus producing precocious coronary sclerosis with narrowing of the lumen, which may cause severe myocardial damage. The abundant myocardial scarring with progressive myocardial disability is better accounted for by coronary narrowing than in any other way." Back in 1906, Aschoff<sup>12</sup> speaking on this subject said: "Healing of the arteritis and periarteritic foci can cause such sclerotic narrowing that ischemic necrosis may result," and he says further "at all events we believe that all scars are due either to plugging of vessels or anemic necrosis and not primarily to interstitial myocarditis."

Acute coronary occlusions occurring in the course of acute rheumatic fever were reported by Kaufmann<sup>13</sup> in 1922, Monckeberg<sup>14</sup> in 1924, and Slater<sup>15</sup> in 1930. There have been a number of cases reported since.

The question has been raised, if we assume a rheumatic basis for the disease in this series of cases, how can the absence of rheumatic valvular disease in all the cases be explained? Hall and Anderson<sup>16</sup> in a recent publication investigated the presence of the so-called rheumatic stigmata in hearts that were free of gross deforming valvular lesions. Using 12 specimens with gross valvular lesions showing all the stigmata in abundance as controls, they studied 112 hearts free of gross valvular lesions and in 90 per cent found rheumatic stigmata. Vascular stigmata were frequently observed. Interesting were their observations relative to the acute vascular changes showing stages of fibrin infiltration and necrosis and the old or chronic stage with hyalinized fibrous wall. They concurred in the belief that the lesions were the result of allergic-hyperergic responses to recurrent upper respiratory infections with the rheumatic virus in persons who are relatively immune. They felt that the hemolytic streptococcus would seem logically to fit the rôle of the rheumatic agent.

Similar lesions have been observed in infections with other streptococcal strains, and Vaubel<sup>17</sup> and later Hemken<sup>18</sup> experimentally produced coronary arteritis with intravenous injections of horse serum. Hall and Anderson<sup>16</sup> emphasized that it is not necessary to demonstrate a specific organism to invoke the allergic hypothesis. They feel that the rheumatic stigmata they demonstrated represented manifestations of allergy to repeated upper respiratory infections with a rheumatic virus.

#### SUMMARY

1. Ten cases presenting cardiac manifestations and characteristic electrocardiographic variations suggestive of an unusual type of cardiac infarction are presented.

2. The cases ranged in age between 20 and 37, the average being 28.4 years; 60 per cent of the group were negroes.

3. All cases gave a history of upper respiratory infections; four of the cases had joint disturbances; five of eight of the cases had high antistreptolysin titers. None of the cases had leukocytosis or polynucleosis, but all had rapid red cell sedimentation rates.

4. The electrocardiographic variations were characterized by T changes with both anterior and posterior wall type of localization, occasional RT changes, and the consistent absence of QRS abnormalities.

5. All the cases improved clinically. The electrocardiograms reverted to a normal pattern in six of the cases and in three the changes improved considerably with the probability that they would in time revert to normal.

6. The upper respiratory infections, the occasional joint disturbances, and the high antistreptolysin titers suggest a rheumatic type of infection.

7. There is general agreement on the occurrence of coronary arteritis in rheumatic infections. Acute inflammatory arteritis characterized by fibrinoid degeneration and late fibrotic changes has been demonstrated. Cases of our series fit into both types clinically.

# CONCLUSIONS

1. The relationship of the upper respiratory infections, occasional joint disturbances and high antistreptolysin titers to the clinical picture and the consistent characteristic electrocardiographic variations suggest a rheumatic or some correlated type of arteritis as the basis for the pathologic lesion in these cases.

2. This study further suggests the possibility that many cases of coronary disease of later life have as their basis an infectious arteritis dating back to their youth.

I wish to express my appreciation to Colonel Arthur R. Gaines, Commanding Officer of Station Hospital, Fort Ord, California, for his assistance and coöperation in preparation of this paper.

# BIBLIOGRAPHY

1. LEVINE, SAMUEL A.: Coronary thrombosis, *Medicine*, 1929, viii, 245.
2. COBURN, A. F.: Faulty disposal of *Streptococcus hemolyticus* in relation to the development of rheumatic lesions, *Trans. and Stud. Coll. Phys. Philadelphia* (4th Series), 1940, viii, 91.
3. JONES, T. D., and MOTE, J. R.: The clinical importance of infection of the respiratory tract in rheumatic fever, *Jr. Am. Med. Assoc.*, 1939, cxiii, 898.
4. HAYEM, G.: Recherches sur les rapports existant entre la morte subite, *Arch. de physiol. norm. et path.*, 1869, ii, 699.
5. MARTIN, H.: Des lesions viscerales consecutives a l'endarterite oblitterante et progressive, *Rev. de med.*, 1881, i, 369.
6. LANDOUZY, L., and SIREDEY, A.: Contribution à l'histoire de l'arterite typhoidique, *Ibid.*, 1885, v, 843.
7. LANDOUZY, L., and SIREDEY, A.: Etude des localisations angio-carideques typoidaques, *Ibid.*, 1887, vii, 919.
8. HUGUENIN, P.: Myocardite infectieuse diphtherique, *Ibid.*, 1883, viii, 999.
9. VON GLAHN, WILLIAM C., and PAPPENHEIMER, ALWIN M.: Specific lesions of peripheral blood vessels in rheumatism, *Am. Jr. Path.*, 1926, ii, 235.
10. KARSNER, HOWARD T., and BAYLESS, FRANCES: Coronary arteries in rheumatic fever, *Am. Heart Jr.*, 1934, ix, 557.
11. BOYD, W.: Pathology of internal diseases, 2nd ed., 1936, Lea and Febiger, Philadelphia.
12. ASCHOFF, L.: Die leutige Lehre von der pathologischanatomischen Grundlagen der Herzschwäche, 1906, G. Fischer, Jena.
13. KAUFMANN: Spezielle pathologische Anatomie, 1922, 1, 42, 7th and 8th Auflage, Berlin u. Leipzig.
14. MONCKEBERG, J. G.: Handbuch d. speziellen pathologischen Anatomie u. Histologie, 1924, Julius Springer, Berlin, ii, 391.
15. SLATER, S. R.: The involvement of the coronary arteries in rheumatic fever, *Am. Jr. Med. Sci.*, 1930, i, 22.
16. HALL, E. M., and ANDERSON, L. R.: The incidence of rheumatic stigmas in hearts which are usually considered non-rheumatic, *Am. Heart Jr.*, 1943, i, 64.
17. VAUBEL, E.: Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindegewebes (II Teil.) Experimentelle Untersuchungen zur Erzeugung des rheumatischen Gewebsschadens im Herzen und in den Gelenken, *Beitr. z. path. Anat. u. z. allg. Path.*, 1932, lxxxix, 374.
18. HENIKEN, L.: Allergy, lesions produced by injection of protein. Read before the Pathology and Bacteriology Section of the California Medical Association at the Sixty-Fifth Annual Session, Coronado, May 25-28, 1936. (Quoted by Hall and Anderson.<sup>10</sup>)

# SYPHILIS AND DIABETES MELLITUS; A LONG-TERM CLINICAL STUDY \*

By FRANK S. PERKIN, M.D., F.A.C.P., *Detroit, Michigan*

THE rôle of syphilis in the etiology of diabetes mellitus has long been a subject of controversy. Isolated cases of the association of the two diseases have appeared in the literature since 1889; some reported apparent improvement in the diabetes following antisiphilitic treatment, whereas others noted a loss of carbohydrate tolerance. The majority of the reports have appeared in the foreign literature where the subject has aroused more interest.

These cases were all subject to the just criticisms that they had not been properly studied from a diabetic standpoint, they had not been observed for an adequate period, and were insufficient in number to justify definite conclusions.

The first case which was properly studied was that of Paullin and Bowcock <sup>1</sup> in 1924. A definite improvement in the diabetic status following anti-siphilitic treatment was demonstrated by glucose tolerance tests and clinical improvement. Unfortunately, this patient died several years later of other causes.

The natural result of the lack of information on such an important subject has been a wide variation of opinion. Lemann <sup>2, 3</sup> felt there was evidence that diabetes in some cases was produced by syphilitic disease of the pancreas, but he believed it was very rare. Recently two extensive studies have appeared which might seem to have closed the subject.

Williams <sup>4</sup> treated 17 cases of syphilis in a group of 1,000 diabetics without finding any evidence of improvement on careful study of their diabetes. In an effort to eliminate all doubtful cases of syphilis, he treated only cases showing other definite clinical evidence of syphilis as well as positive serologic reactions. It is my belief that he thus eliminated the group which is of most importance, i.e., the tertiary and latent syphilitic without other evidence of syphilis. His statement that severe diabetics with low carbohydrate tolerance requiring large doses of insulin frequently show subpositive Wassermann reactions with one or more antigens has not been verified in my experience or that of other observers. His findings thus would merely verify those of other students that in no cases of early or active syphilis was there any effect on the diabetes from anti-siphilitic treatment.

McDaniel, Marks and Joslin <sup>5</sup> have made a very complete statistical study of 258 cases of syphilis found in Joslin's group of 15,095 diabetic patients. There is included a very complete review of the literature and statistical data to which students of the subject may refer, and which make repetition unnecessary. From their analysis of this series, they were unable to find a

\* Received for publication March 20, 1943.

From the Diabetic Service, Receiving Hospital, Detroit, Michigan.

single instance of cure of diabetes brought about by optimum anti-syphilitic treatment. Of interest was their conclusion that, theoretically, if "syphilitic diabetes" occurs, it would most likely be a late manifestation of syphilis occurring in older persons.

In the belief that the controversial opinions on the rôle of syphilis in diabetes were the result of lack of evidence based on prolonged observation and sufficient material, in 1928 a study of the problem was initiated. This was stimulated by the discovery of several cases of association of the two diseases which exhibited apparently an unusual improvement in their diabetic status while on antisyphilitic treatment. At Receiving Hospital, Detroit, there was an exceptional opportunity for such an investigation, with a large volume of diabetic patients from a section of society in which syphilis is unusually common. Also, these patients, because they received free treatment and insulin, were under observation for extended periods.

This report is based on personal observation in the majority of cases, and study of the records in the remainder, of all diabetics, 644 in number, attending Receiving Hospital and seen in private practice between 1928 and 1933, with a follow-up study in the succeeding years of such cases of interest as could be induced to continue under study and treatment.

This series is represented by the following statistics.

TABLE I

Total cases of diabetes.....	644	
No syphilitic serologic tests.....	94	
Cases included in this series.....	550	
Cases with positive syphilitic serologic tests.....	42	7.6%
Cases with positive history but negative serologic tests.....	12	2.2%
Total cases of possible syphilis.....	54	9.8%

The 94 cases without serologic tests represent cases which were hospitalized for very short periods, deaths shortly after admission, negligence in completing the examination, and various other causes. These cases were eliminated from consideration in the analysis.

The 42 definite and 12 probable cases represented the group in which anti-syphilitic therapy might prove to be of value.

TABLE II

Total cases in this series—550

	Syphilitic Group	Non-Syphilitic Group
Colored— 88	20—23%	68—77%
White—462	34— 7.4%	428—92.6%
Males—251	23— 9%	228—91%
Females—299	31—10.4%	268—89.6%

The colored cases constituted 37 per cent of the syphilitic diabetics and 14 per cent of the non-syphilitic diabetics. This only serves to demonstrate the greater incidence of syphilis in the colored race and has no definite bear-

ing on the present problem. The 9.8 per cent of our total diabetic cases with a syphilitic history closely conforms to the percentage in all Receiving Hospital admissions, and this might be taken as evidence against any etiological relation between syphilis and diabetes. On the other hand, it is to be considered that many hospital admissions are the result of conditions which are recognized as later manifestations of syphilis. Thus, the percentage of syphilitics in all cases of heart disease also is not greatly at variance with the percentage in all admissions. I do not believe that this method of analysis can be depended upon to give reliable evidence.

The distribution of cases between male and female is about even. This is at variance with the findings in McDaniel's <sup>5</sup> analysis of Joslin's series, but probably has no marked significance. However, it has been my impression that if syphilis is of significance in the diabetic, it is more likely to be in the diabetic female.

TABLE III  
Age Groups

	1 to 30	30 to 40	40 to 50	50 to 60	60 and over
Non-Syphilitic Group....	10.5%	18.5%	20%	27.7%	24%
Syphilitic Group.....	2.3%	14.5%	35%	30.0%	17.5%

A very interesting observation is found in the study of the classification by age groups. The non-syphilitic group conforms to the usual findings in any series. The syphilitic group is concentrated in the later decades of life. Of the two cases under 30 years of age one was a known diabetic before contracting syphilis.

TABLE IV  
Degree of Severity of Diabetes

	Mild	Moderate	Severe
Non-Syphilitic.....	131—26%	280—57%	85—17%
Syphilitic.....	30—55.5%	18—33.5%	6—11%

For purposes of classification, a mild diabetic was considered a case which did not require insulin on a maintenance diet, a moderate diabetic one who did not require more than 20 units of insulin daily, and a severe diabetic, one requiring more than 20 units of insulin daily. Although admittedly this is not an exact method, it affords figures for comparison. The syphilitic group is remarkable for the preponderance of mild cases, and severe cases in this group include one case that was known to have contracted his syphilis while diabetic. Because of the mildness of their diabetes and lack of symptoms, it was, as a rule, difficult to persuade these patients to continue a long course of treatment, and many after a short period would not return, stating they felt perfectly well.

In Joslin's series, based on a slightly different classification, 65.9 per cent were mild, 19 per cent moderate, and 8.9 per cent severe. The figures for the whole group are not given. In the present series the variation in severity of the diabetes between the non-syphilitic and syphilitic groups would appear to hold some possible significance.

TABLE V  
Other Pathologic Lesions Resulting from Syphilis

	Cases
A. Central nervous system involvement.....	5
B. Cardiovascular involvement.....	1
C. Skin involvement.....	1

Few of these cases showed other pathologic lesions as a result of their syphilis.

This is in accord with the usual findings in tertiary syphilis. In view of the number found to have central nervous system involvement, spinal fluid studies should have been done in a larger percentage of cases.

TABLE VI  
Response to Treatment

Cases in syphilitic group given antisyphilitic treatment.....	19
Cases showing varying degrees of improvement in tolerance following antisyphilitic treatment.....	14
Cases showing no improvement in tolerance following antisyphilitic treatment...	5

The comparatively small percentage of cases which are included in the above summary is the result of including only those cases which were judged possibly to fall in the group where the association of the two diseases might be significant and which were treated and observed over an extended period. The cases in which no change in diabetic status occurred after adequate antisyphilitic therapy were regarded as cases in which the association of syphilis and diabetes was merely incidental. Some of the cases in which changes occurred will be described as giving possible evidence in the problem of etiological relationship.

*Case 102.* M.S., female, white, aged 54, weight 134 lbs., was first seen in February, 1929. She had been a known diabetic for over two years and was under treatment at the North End Clinic, where she had been on a diet and 15 units of insulin for several months. Her past history included typhoid fever in 1917. There was no family history of diabetes. She was admitted to Receiving Hospital for observation and discharged on a diet of CH. 90, P. 50, F. 140, with 10 units of insulin daily. She had been found to have positive Kahn and Wassermann reactions. Her glucose tolerance test at this time is shown in figure 1. She commenced antisyphilitic treatment and was given one course of arsenicals at the Board of Health. Following this she was treated at our clinic for a year with iodides, bismuth, and a further course of arsenicals.

In August, 1929, she was having occasional insulin reactions although not following her diet, and the insulin dosage was reduced to 5 units daily. In December, 1929, insulin was discontinued. The Wassermann reaction at this time was negative. A glucose tolerance test in February, 1930, was regarded as normal. From this time until 1935, she was without clinical or laboratory evidence of diabetes. Early in 1935,



she commenced to show abnormally high blood sugar readings and a tolerance curve in February, 1936, demonstrated a diabetes more severe than at any time during our observation. Kahn reaction at this time was negative. In December, 1941, she was still a severe diabetic, requiring 40 units of protamine zinc insulin and 10 units of regular insulin daily for control.

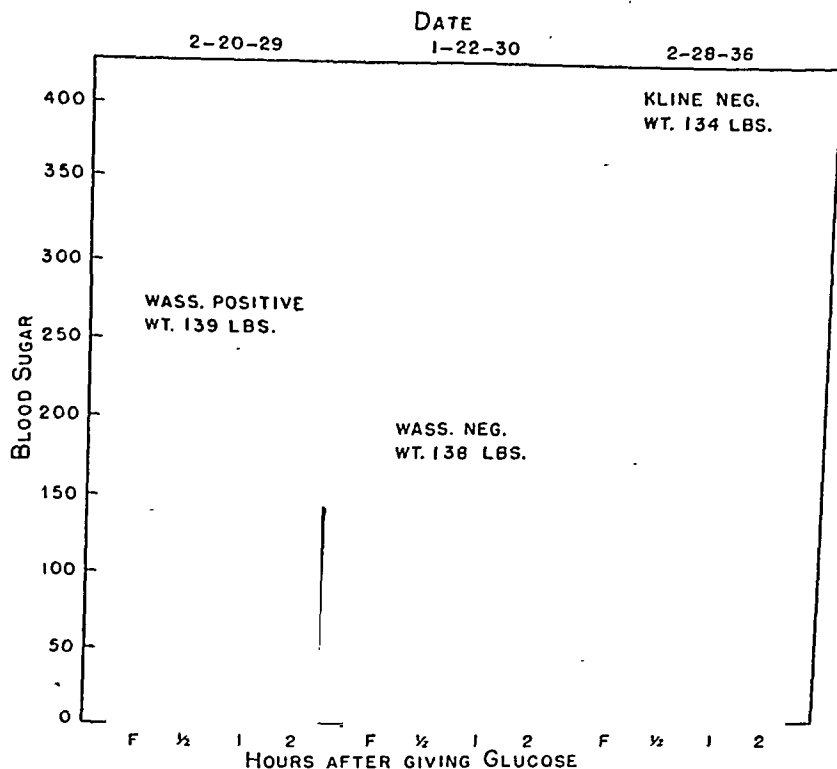


FIG. 1. M. S., female, aged 54 years, height 5' 1", standard weight 134 pounds, duration of diabetes 2½ years.

In this case there was demonstrated an improvement in the glucose tolerance to a point which might be regarded as non-diabetic, which it was difficult to ascribe to other causes than the antisiphilitic therapy. This improvement persisted for about five years, when the diabetes again became manifest and in a more severe degree, although the serologic tests for syphilis remained negative. None of the other so-called etiological factors could be demonstrated.

*Case 356.* J. W., female, colored, aged 40, weight 156, was first seen November, 1930. She had been told she had diabetes four months before, and her diabetes had not been controlled by a diet. There was no family history of diabetes. Her past history was unimportant except for one miscarriage and two stillbirths. Physical examination was negative with no clinical signs of syphilis. The Wassermann reaction was positive.

She was hospitalized for observation and discharged on a diet of CH. 90, P. 60, F. 120, with 20 units of insulin daily. The glucose tolerance test at this time is shown in figure 2. She was given antisiphilitic treatment consisting of bismuth, iodides, and one course of arsenical over a period of nine months, during which insulin was grad-

ually discontinued, although the patient was not following her diet. Following this she was seen at long intervals, showing normal blood sugar readings and no evidence of diabetes. Her Wassermann reaction was negative, and no further antisyphilitic treatment was given. In January, 1936, she commenced to show higher blood sugar levels, and complained of pain in the upper abdomen. On a diet of CH. 120, P. 70, F. 130, she required 5 units of insulin daily. Examination showed some liver enlargement, more marked in the left lobe. Gastrointestinal series showed no disease, and a glucose tolerance test gave a curve indicative of mild diabetes, although much better than five years previously. Her Kline reaction was positive, Kahn doubtful and

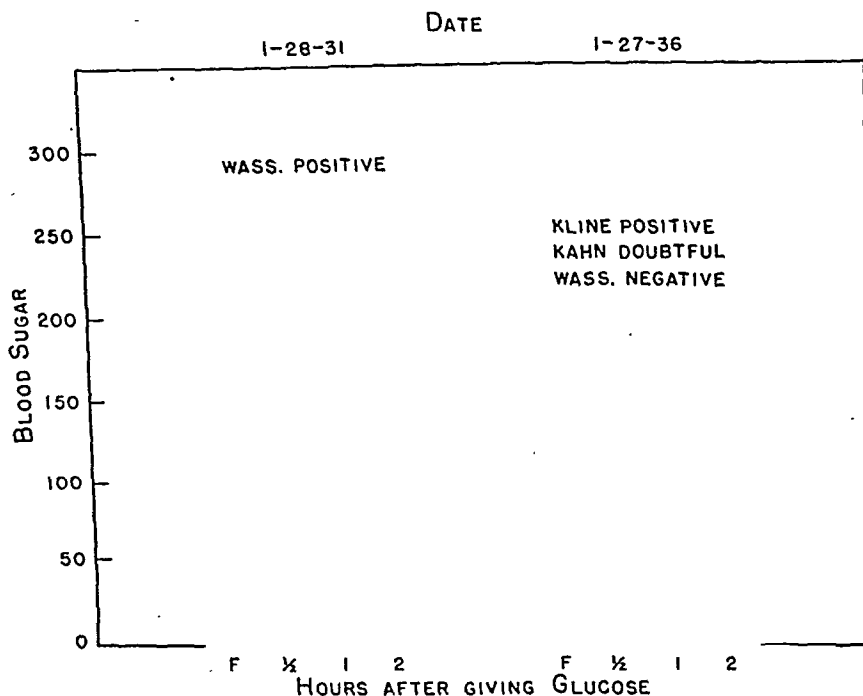


FIG. 2. J. W., female, aged 40 years, height 5' 3", standard weight 156 pounds, duration of diabetes 6 weeks.

Wassermann negative. In September, 1936, there was some persistence of upper abdominal pain. Gall-bladder roentgenograms showed no visualization following dye administration. She improved on medical treatment but required 15 units of insulin daily. There was no apparent response to further antisyphilitic treatment, either on the part of her diabetes or liver enlargement. Operation for possible gall-bladder disease was refused. In April, 1939, gall-bladder roentgenogram still showed non-visualization. In December, 1941, she was well controlled on 10 units of protamine zinc insulin daily.

This case showed an unusual improvement in the severity of her diabetes while on antisyphilitic treatment. The increase in severity some years later was associated with evidence of liver damage and a non-visualizing gall-bladder. The serologic tests for syphilis showed subpositive responses to some antigens. The lack of response to antisyphilitic therapy, however, suggests that some other etiological factor was now present, possibly a chronic cholecystitis.

*Case 604.* A. J., male, white, aged 49, weight 156, was first seen June, 1932. He had been rejected for life insurance one week previously following a glucose tolerance test. Important points in his history were a chancre 30 years before with one short course of treatment only, and the fact that his wife had numerous miscarriages before bearing living children. There was no family history of diabetes. His physical examination was essentially negative with no clinical manifestations of syphilis. The fasting blood sugar was 208 mg. A glucose tolerance test showed a definitely diabetic type of curve. His first Kahn reaction was negative. Following provocative treatment with iodides and arsenicals, one of two Kahn reactions was reported as positive. He was not placed on a diet and was given antisyphilitic treatment, iodides, bismuth, and a short course of arsenicals until December, 1932, when a glucose tolerance test gave a normal type of curve. Blood sugar levels were consistently normal. Treatment was continued until August, 1933, during which period there were no abnormal

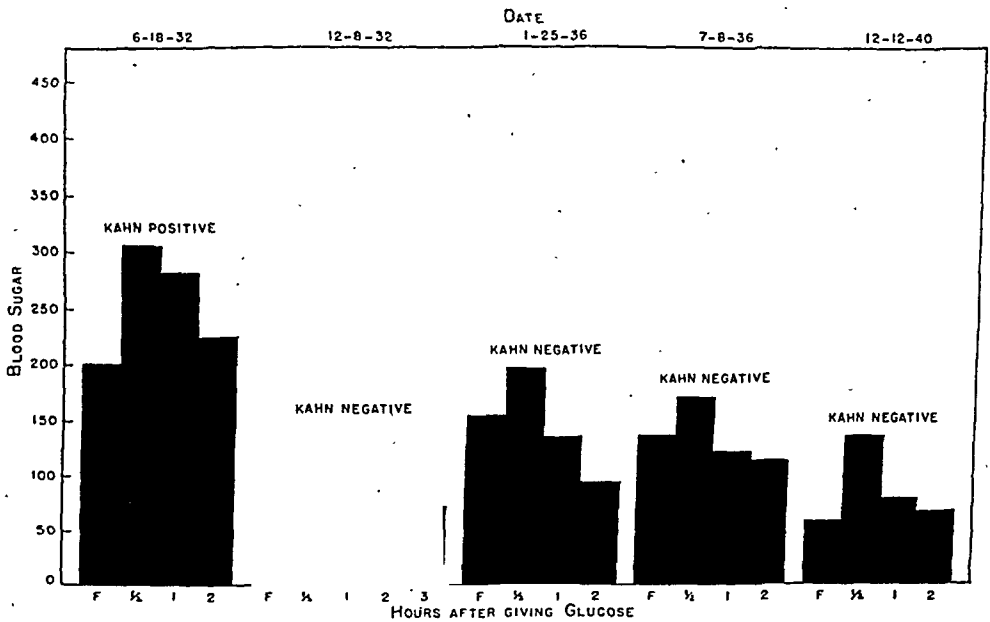


FIG. 3. A. J., male, aged 49, height 6', standard weight 163 pounds, duration of diabetes unknown.

blood sugar levels, despite the fact that he had refused to accept welfare assistance and was living largely on bread and potatoes. He was seen at intervals until January, 1936, when he again showed a slight glycosuria, and a glucose tolerance test showed a mildly diabetic curve. He was given a further course of bismuth injections, continuing on an unrestricted diet. A curve in July, 1936, suggests a possible effect from this treatment. He was seen on rare occasions until December, 1940, when an unquestionably normal type of curve was obtained on a glucose tolerance test. Variations in weight from 1932 to 1940 never exceeded five pounds. In December, 1941, the blood sugar, after a high carbohydrate meal, was 82 mg.

This case in most series would be regarded as showing inadequate evidence of syphilis, yet if he had shown an aneurysm, for instance, its syphilitic origin would not have been doubted. It is difficult to explain this improvement on any other basis than that of his antisyphilitic therapy, as he received

no diabetic treatment, either diet or insulin. He is also one of the rare cases in which the diabetes is not manifest after a 10 year period, although experience with other cases suggests that it might recur at any time.

*Case 127.* A. W., female, white, aged 50, is perhaps the most interesting and instructive case. She was first seen in April, 1928, weight 270 pounds, a known diabetic for five years, poorly controlled but never had received insulin. Her past illnesses and family history were not of note. Her physical examination, except for her marked obesity and a ventral hernia, showed no significant findings. Her fasting blood sugar varied between 150 and 200 mg. She had positive Wassermann and Kahn reactions. She was placed on a low carbohydrate diet of CH. 60, P. 75, F. 125, similar to diets that she had presumably been following for several years. No insulin was given and antisyphilitic therapy was instituted. She received two courses of neo-

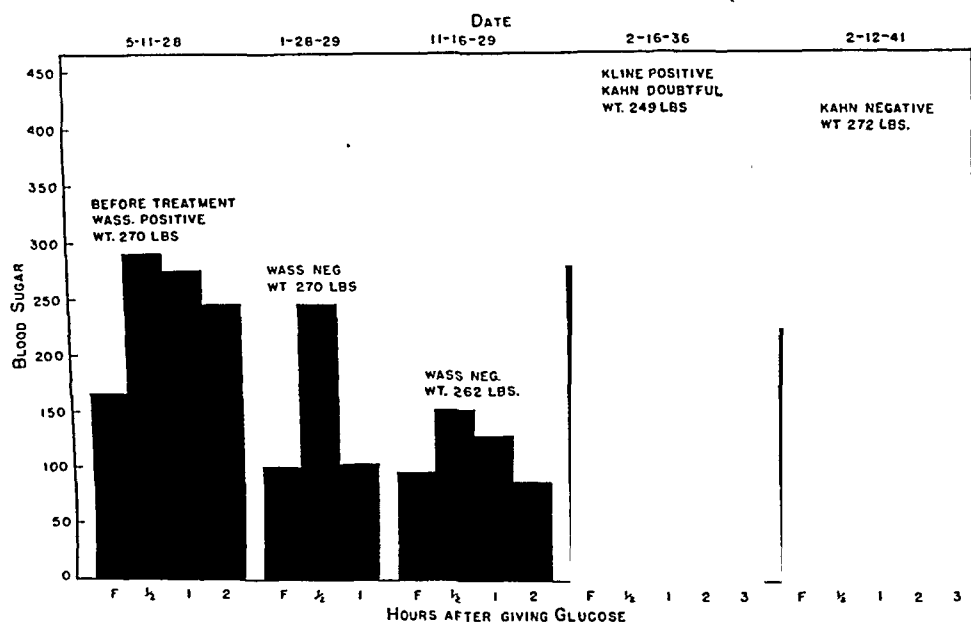


FIG. 4. A. W., female, aged 50, height 5' 6", standard weight 260 pounds, duration of diabetes 5 years.

salvarsan and continuous bismuth injections over a period. She slowly lost weight until in January, 1929, she weighed 252 pounds. Her Wassermann reaction was negative, and she was definitely improved from a diabetic standpoint. At this time she discontinued following a diet, and antisyphilitic therapy was continued in the form of bismuth intramuscularly and iodides. In November, 1929, she had gained to 262 pounds, was not on a diet or receiving insulin and was apparently non-diabetic to all tests. She was seen at intervals over the next few years, with at all times a normal fasting blood sugar. During this time she was confined to another hospital for her ventral hernia, where after tolerance tests, she was told she was non-diabetic.

She was lost to my observation for several years, but in 1934 returned to our clinic with a definite return of her diabetes. It is of interest to note that at this time she showed a positive Kline reaction and negative Kahn and Wassermann reactions. Her diabetes slowly increased in severity, and in 1935 she was placed on insulin. In October, 1935, she showed a positive Kline and a doubtful Kahn reaction. In February, 1936, the severity of her diabetes as evidenced by a glucose tolerance curve

was greater than at any time during our observation. In December, 1937, she was a very severe diabetic, requiring a total of 80 units of regular insulin daily and, incidentally, the only diabetic under my observation unable to use protamine zinc insulin because of local inflammatory reactions. She had received several courses of anti-syphilitic treatment in 1936 and 1937 and showed some improvement in her diabetes. In September, 1940, she was admitted to hospital showing a mild gangrene of one leg. She was controlled on 10 units of protamine zinc insulin daily. In February, 1941, there was a recurrence of her gangrene, with an increase in the severity of her diabetes, as shown in chart 4. In June, 1941, she died suddenly presumably of cardiac disease in a private home. An autopsy was not obtained.

In this case I felt that all other reasons for improvement than anti-syphilitic therapy could be eliminated. This improvement was of such a degree that she was regarded as non-diabetic for some five years. That the recurrence was the result of her syphilis is open to some question, as it is quite possible that a further etiological factor, e.g., her obesity, was now playing a rôle. It is significant that her marked obesity had persisted with little change through the 13 years of my observation.

The technic of the glucose tolerance tests used in these charts consisted in the administration of 1.75 grams of glucose per kilo of actual body weight. The use of glucose tolerance curves in these cases to demonstrate changes in the degree of diabetes present is undoubtedly subject to criticism based on the known variations that may occur in these curves from other causes. Despite this, they still constitute a valuable method of comparison, and, when accompanied by other clinical and laboratory evidence, are undoubtedly significant.

One phase of this problem is perhaps even more controversial, and that is the relationship between syphilis and gangrene in the diabetic. It has been felt by many workers that there might be some connection, and Joslin<sup>6</sup> has apparently changed his opinion on the subject several times during the years, although his latest review denies any relationship. It has been surmised that the diabetic with tertiary syphilis may be more prone to have arterial disease and hence more likely to develop gangrene. This is a logical possibility and would appear to be borne out in this series where by using extensive methods of inquiry and investigation, syphilis was regarded as a factor in 16 of 74 cases of gangrene. This is an unusually high percentage and was only obtained by including some doubtful cases, and yet it was in some of these cases that the most significant results were obtained from antisyphilitic therapy.

*Case 63.* G. M., male, white, aged 60, was admitted to Highland Park Hospital, January, 1931, with gangrene of the left foot. He had been a mild diabetic for five years. Wassermann reaction was negative. Despite good control of his diabetes on diet and 40 units of insulin daily, the gangrene was progressive and amputation was performed above the knee. The stump did not heal and gangrene appeared in the right foot. Persistent questioning finally elicited a history of a penile sore and "blood treatments" in 1910. Following provocative therapy, a sub-positive Kahn reaction was obtained. On continued antisyphilitic treatment the stump commenced to heal and gangrene in the right foot disappeared. He was discharged on 35 units of insulin

daily and antisyphilitic therapy continued. His diabetic status gradually improved until in February, 1932, he was showing persistently normal blood sugar levels on a liberal diet without insulin. He was next seen by another physician in 1934 in a severe delirium tremens with a story of alcoholism over a period of several months. He had not been on a diet for several years. There was no glycosuria and fasting blood sugar was 112 mg. His further course is unknown.

### TREATMENT

These cases were treated for their diabetes in a routine manner according to the methods of 1928-1933, with the exception of certain selected cases in which neither diet nor insulin was used. Here an effort was made to eliminate possible improvement from other causes than antisyphilitic therapy.

The treatment followed was the usual routine for tertiary syphilis. Bismuth salicylate was the drug of choice, used in one or two weekly injections over long periods. Iodides were used freely, at times being the only drug used. No benefit was noted from the use of iodides alone. Mercury was not used in most cases. Arsenicals were used when and where indicated, the majority of the treated cases receiving one or two courses. No ill effects were noted from arsenicals. It is my impression that the belief that the use of arsenicals is contraindicated in diabetes dates back to the pre-insulin days, when the poorly controlled diabetic with a low glycogen reserve was very likely to develop liver damage. Generally speaking, our present day diabetic, even of a severe grade, tolerates arsenicals well.

### PATHOLOGY

Two cases only in this series have come to postmortem examination.

*Case 152.* F. B., male, white, aged 44, was treated for syphilis at age of 18. He was a severe diabetic. Wassermann reaction on admission to the hospital was negative. He died of a ruptured gastric ulcer. The pancreas showed no significant changes, the liver a toxic hepatitis, probably the result of his peritonitis. There was no evidence of his previous syphilitic infection.

*Case 62.* J. P., male, white, aged 46, was a mild diabetic with a positive Wassermann reaction. He died of pyonephrosis. Autopsy showed no abnormalities in the pancreas. There was described a peculiar diffuse round cell infiltration in the liver with capillary congestion. There were lesions suggestive of syphilis in the heart and kidneys.

No conclusions can be based on such inadequate data, but the findings are of some interest. The possible rôle of syphilis in diabetes is purely speculative. The findings of Warthin and Wilson<sup>7</sup> in 1916 of syphilitic pancreatitis have never been duplicated. Warren in his series had no cases in which he felt that syphilis could be responsible for the changes found in the pancreas. It is probably correct to state that syphilitic pancreatitis which has been searched for as the probable pathologic lesion in cases of the association of syphilis and diabetes is rarely, if ever, present. In recent

years, however, it has been realized that the etiology of diabetes is more complex than simple pancreatic disease, dysfunction or deficiency, and tertiary syphilis may play a significant rôle in other ways.

Warren includes in his classification of anatomical causes of insulin deficiency inadequate blood supply or arteriosclerosis, although few such cases were seen in his series. This might represent the mechanism by which the pathologic lesions of tertiary syphilis could influence the severity of a diabetes. This theory is lent some weight by the increased proportion of syphilitic diabetics who develop gangrene.

The liver must be considered as a possible site of damage in certain of these cases, and central nervous system involvement may be responsible in others. More intensive postmortem studies in such a group of cases would be of great value.

### DISCUSSION

The collection of a more adequate group of cases of syphilis in association with diabetes, and a prolonged period of observation of such cases make certain phases of the subject more distinct. The time factor in the study of such a problem in diabetes is of great importance, as conclusions drawn at the end of a four year period of study of these cases were later shown to be erroneous.

Diabetes is not affected by the primary or secondary manifestations of syphilis to any greater degree than by other systemic infections. Whatever rôle syphilis may play is distinctly associated with the tertiary or latent stages of the disease; thus, the argument that diabetes should occur in congenitally syphilitic children is not valid. In this series where treatment was concentrated on a group of diabetics with some evidence suggesting latent or tertiary syphilis, unusual improvement in carbohydrate tolerance was observed in some cases where all other reasons for such improvement than the anti-syphilitic treatment could be eliminated. These were frequently cases which ordinarily would not receive antisymphilitic treatment because of the lack of other evidence of syphilis. In the effort to find these latent cases it is possible that some non-syphilitics were treated.

Of utmost importance was the finding brought only by years of observation that the majority of the cases showing improvement, at some later date again showed an increase in the severity of their diabetes. Despite the one case which shows no evidence after almost 10 years of observation, I believe that the dictum "once a diabetic always a diabetic," still holds, with the exception that I would add "once a diabetic, always a potential diabetic."

Much more consistent and dramatic results have been described by Newburgh and Conn<sup>8</sup> in a group of obese diabetics, where studies of 21 cases before and after weight reduction showed definitely diabetic types of curves reverting to normal in all cases. In a later paper,<sup>9</sup> Newburgh reports that 77 per cent of adult obese hyperglycemic patients, 47 in all, showed normal glucose tolerance tests after adequate weight reduction. It must be em-

phasized that Newburgh does not regard this group as instancing true diabetes. Dr. Frank Allen, in discussing this work, suggested the advisability of reporting the fate of these cases after five, or even 20 years. The 20 year period would not be too long if my experience with the present series is taken as a criterion. The authors, however, made the valuable observation that attributing diabetes to a pancreatic abnormality is far too restricted a conception, and that clinical investigators must now attempt to discover the specific cause of the hyperglycemia in all patients who present the classic signs and symptoms of the disease to which the term "diabetes" is attached.

Observation of the syphilitic group has led to consideration of the theory that diabetes rarely, if ever, develops in an individual who is not born with a potential defect in carbohydrate metabolism. At one time I would have attributed the potential defect to a low reserve insulin production, but the problem has become much more complex with our knowledge of the rôle of the pituitary gland and liver. Many of such potential diabetics may never develop diabetes, whereas others as a result of the presence of any of the classical so-called causes of diabetes, as obesity, hyperthyroidism, gall-bladder disease, etc., would develop clinical signs of diabetes. With the treatment and removal of these precipitating factors, they might again become clinically non-diabetic until such time as further damage occurred or unusual strain was thrown on their insulogenic mechanism. This has been demonstrated in obesity, in gall-bladder disease, in hyperthyroidism, and, I believe, this series suggests that similar results may occur in tertiary syphilis.

#### SUMMARY

By exhaustive investigation for the presence of latent as well as active syphilis, 54 possible cases of syphilis were found in a group of 550 diabetics seen at Receiving Hospital, Detroit. Factors of color and sex were relatively unimportant, but the presumably syphilitic group was unduly concentrated in the later decades of life. The diabetes in the syphilitic group tended to be unusually mild.

Nineteen cases of latent or tertiary syphilis were given prolonged anti-syphilitic treatment under careful observation and, where possible; this was followed by glucose tolerance tests. In some cases, when feasible, no diabetic treatment, as diet or insulin, was prescribed. These cases were then observed for varying periods up to 12 years for changes in their diabetic status. Fourteen cases showed varying degrees of improvement in tolerance, from moderate to a degree where apparently no diabetes was present. In one case no evidence of diabetes was present after 10 years.

The series suggests that there is some relationship between latent syphilis in the diabetic and the occurrence of gangrene. Syphilis should be suspected in the mild diabetic who develops gangrene, even in the presence of a negative serologic reaction. Careful histories and studies of the effect of anti-syphilitic therapy may be necessary.



Even where the most marked improvement was found, there was a tendency in later years for the diabetes to reappear. It is suggested that tertiary syphilis, as well as all other so-called causes of diabetes; is merely a precipitating factor in the potential diabetic.

Note: The word "diabetes" is used to apply only to diabetes mellitus.

#### BIBLIOGRAPHY

1. PAULLIN, J. E., and BOWCOCK, H. M.: Treatment of syphilis co-existent with condition simulating diabetes, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 702-705.
2. LEMANN, I. I.: Diabetes mellitus, syphilis and the negro, *Am. Jr. Med. Sci.*, 1921, clxii, 226.
3. LEMANN, I. I.: Relation of syphilis and diabetes to one another, *Am. Jr. Syph.*, 1929, xiii, 70.
4. WILLIAMS, J. R.: Diabetes and syphilis . . . a critical study of relation to each other in 1000 cases of diabetes, *N. Y. State Jr. Med.*, 1941, xli, 252-255.
5. MCDANIEL, L. T., MARKS, H. H., and JOSLIN, E. P.: Diabetes mellitus and syphilis: study of two hundred and fifty-eight cases, *Arch. Int. Med.*, 1940, lxvi, 1011-1051.
6. JOSLIN, E. P., ROOT, H. F., WHITE, PRISCILLA and MARBLE, ALEXANDER: Treatment of diabetes mellitus, 6th Ed., 1937, Lea and Febiger, Philadelphia.
7. WARTHIN, A. S., and WILSON, V. F.: Coincidence of diabetes and syphilis, *Am. Jr. Med. Sci.*, 1916, clii, 157.
8. NEWBURGH, L. H., and CONN, J. W.: A new interpretation of hyperglycaemia in obese middle-aged persons, *Jr. Am. Med. Assoc.*, 1939, cxii, 7.
9. NEWBURGH, L. H.: Control of the hyperglycaemia of obese "diabetics" by weight reduction, *ANN. INT. MED.*, 1942, xvii, 935.

# CIRRHOSIS OF THE LIVER; AN ANALYSIS OF 71 CASES\*

By I. DONALD FAGIN, M.D., and FRANK M. THOMPSON, M.D.,  
*Detroit, Michigan*

THIS study represents an analysis of 71 patients with portal cirrhosis observed at the U. S. Marine Hospital, Detroit from 1926 to the present, with particular reference to clinical manifestations. An excellent comprehensive review of the natural history of Laennec's cirrhosis of the liver has been published recently by Ratnoff and Patek,<sup>1</sup> who included a bibliography of the recent literature. In order to avoid duplication, we shall limit our comments primarily to statistical analysis of the case material, with but brief amplification upon theoretical considerations.

## MATERIAL

The 71 cases analysed consist of 21 cases wherein the diagnosis of portal cirrhosis was confirmed by liver biopsy (three cases) or by autopsy (18 cases), and 50 cases with strong presumptive evidence of portal cirrhosis; cases in which the diagnosis was equivocal were excluded. Two cases of hemochromatosis and one case of cirrhosis following carbon tetrachloride poisoning were observed during the same period, but they are not included in this series because they could not be classified as portal cirrhosis.

Of the 71 patients, 29 died in the hospital and 42 were sufficiently improved to be discharged from the hospital. In view of the migratory nature of the clientele of the hospital, follow-up studies are unsatisfactory, and conclusions must, therefore, be drawn from the hospital records only in the majority of instances.

## ETIOLOGIC FACTORS

(1) *Age.* The age distribution of the patients by five-year groups is presented in table 1. The average age on admission of the 71 patients

TABLE I  
Age Distribution of 71 Patients with Cirrhosis of the Liver

Years	Number of Patients
36-40 .....	9
41-45 .....	14
46-50 .....	24
51-55 .....	16
56-60 .....	4
61-65 .....	2
66-70 .....	1
71-75 .....	1

\* Received for publication May 24, 1943.

From the Medical Service of the U. S. Marine Hospital, Detroit, Michigan.

was 48.4 years, the youngest being 36 years old, and the oldest 73 years. It is apparent that the majority of the patients (54, or 77 per cent) was between the ages of 41 and 55 years, the peak of incidence being between 46 and 50 years, which is in fairly close agreement with the findings of others.<sup>1,2</sup> Therefore, it is evident that the incidence is maximal in the fifth and sixth decades.

(2) *Race*. Of our 71 patients, 22 (31 per cent) were of American descent, 12 (17 per cent) of German descent, eight (11 per cent) of Irish descent, seven (10 per cent) of Polish descent, and two (3 per cent) each of Belgian and Italian descent; the other 18 patients were of mixed or unknown descent. The racial incidence of portal cirrhosis is of uncertain significance as an etiologic factor in any one reported series, since the reported incidences must be corrected in the light of the racial distribution of the hospital population.

(3) *Sex*. All of our 71 patients were males; however, since less than 10 per cent of our hospital population is female, we can draw no conclusions as to sex incidence. (The usually accepted ratio is two or three males to each female with cirrhosis of the liver.)

(4) *Occupation*. Nineteen of the patients were merchant seamen, who are usually "spree" drinkers; 24 were laborers; and five were bartenders. The remaining 23 patients were engaged in miscellaneous occupations. The rather high incidence of seamen is due to the selection of beneficiaries of the Marine Hospital Division of the U. S. Public Health Service. The high incidence among laborers and bartenders is in accordance with accepted experience.

(5) *Alcoholism*. The consumption of alcohol by the patients studied is summarized in table 2. It is apparent that 56 of the 71 patients (79 per

TABLE II  
Alcohol Consumption of Patients with Cirrhosis

Consumption of Alcohol	Number of Patients
1. Abstainers.....	7
2. Occasional drink (beer or whiskey).....	8
3. Habitual indulgence.....	
(a) In moderation (e.g., 2-4 drinks daily).....	8
(b) Moderately excessive (e.g., 5-7 drinks daily).....	17
(c) Excessive indulgence.....	31

cent) were habitually addicted to the use of alcoholic beverages. One of the patients, a 63 year old tavern keeper, admitted drinking about one pint of whiskey, 20 to 30 glasses of beer, and 10 to 12 glasses of wine daily for about 30 years, and there was little reason to doubt his veracity.

The significance of alcoholic indulgence as a factor in producing cirrhosis of the liver has long been a moot question and it would serve no purpose to repeat here the arguments pro and con, since the subject has recently been reviewed thoroughly by Jolliffe and Jellinek.<sup>3</sup> They concluded that the association between chronic alcoholism and cirrhosis is definitely established, but

that alcohol is not a *direct* cause of cirrhosis, and none of the theories of *indirect* causation heretofore advanced (i.e., exogenous toxins other than alcohol present in alcoholic beverages, gastric disturbances, general metabolic disturbances of toxic nature, vitamin deficiencies, or transition from fatty liver to cirrhosis) is, of itself, sufficient to explain the association. The investigations of Connor<sup>4, 5</sup> indicate that excessive indulgence in alcohol may lead to fatty infiltration of the liver by virtue of the toxic action of alcohol on tissue oxidative processes, plus the relative starvation and the vitamin deficiencies which are so frequently found in association with chronic alcoholism. The fatty infiltration may cause atrophy and degeneration of the liver cells, with subsequent replacement by fibrous tissue and the development of hepatic cirrhosis.

In our series, fatty infiltration in association with portal cirrhosis was present in eight out of 21 livers examined microscopically. However, the absence of fat cannot be used as an argument against the significance of fatty infiltration of the liver as a step in the pathogenesis of cirrhosis, because terminal exhaustion of body fat, or the cessation of indulgence in alcohol, or the use of a high-protein, high-carbohydrate diet or other lipotropic factors may promote resorption of liver fat.<sup>4, 6</sup>

(6) *Syphilis*. Nineteen (27 per cent) of the patients in this group had positive blood Kahn reactions, or a history of a primary lesion, or both. Only six of these patients had received arsenical antisyphilitic therapy previously. Schumacher<sup>7</sup> reviewed the significance of syphilis as a causative factor in cirrhosis of the liver and concluded that syphilis with, and possibly without, associated alcoholism may cause a diffuse cirrhosis of the liver.

Of the 19 patients in this series with evidence of syphilis, 18 were habitual imbibers of alcoholic beverages. The actual coexistence of alcoholism and syphilis in this series is 25.4 per cent, whereas the chance expectancy of such coexistence is 21.1 per cent. None of the livers examined presented a picture typical of syphilitic cirrhosis.

What significance the use of arsenicals in the treatment of syphilis may have in the development of cirrhosis is not clear, since 13 of the 19 patients who had syphilis and cirrhosis had not been treated with arsenicals. The crux of the problem is aptly presented by Baldridge: "Vices are prone to be multiple, so that alcoholism, syphilis, and antisyphilitic treatment often coexist in the history of patients with cirrhosis of the liver."<sup>8</sup>

(7) *Heart Disease*. Organic heart disease was present in 10 of the 71 cases, 15 per cent (one case of rheumatic heart disease, two of hypertensive heart disease, and seven of arteriosclerotic heart disease). However, in only four of these cases was there evidence of congestive heart failure. The detection of congestive failure in association with cirrhosis of the liver is a difficult clinical problem, since dependent edema is common in cirrhosis, and dyspnea and orthopnea may result from ascites or hydrothorax in cirrhosis. Katzin and his co-workers<sup>9</sup> have reviewed "cardiac cirrhosis" and con-

cluded that it is clinically a relatively rare condition, although chronic passive hepatic congestion secondary to congestive heart failure frequently causes an increase in hepatic fibrous tissue. The fibrosis may be central or portal or both, and is directly proportionate to the duration of the heart failure.

Each of the four patients in our series who had congestive heart failure and cirrhosis was also a habitual alcohol imbibor, so the influence of the cardiac factor in this series is highly equivocal.

(8) *Previous Hepatic Disease.* Only one patient in this series had a history of an episode of previous jaundice, which occurred 28 years prior to his hospitalization with cirrhosis.

The conception of cirrhosis as an inflammatory process which may be acute or chronic and may have long periods of latency has been advanced.<sup>10</sup> The possibility that an infectious process may be responsible for the inflammatory changes described in some cases of cirrhosis<sup>11</sup> is unproved. The occurrence of fever, leukocytosis, and elevated erythrocyte sedimentation rates in many of the patients in this group tends to support the concept of the inflammatory character of the pathologic process, at least in certain cases.

(9) *Toxic Agents.* The six patients who received arsenical antisyphilitic treatment have already been mentioned, and each of these patients was a chronic alcohol addict; therefore, the influence of arsenic in this series is questionable, except that the arsenicals may have rendered the liver more susceptible to the toxic action of alcohol (or vice versa).

None of the 71 patients with portal cirrhosis presented here had a history of exposure to lead, cinchophen, chloroform, tetrachlorethane, copper, or other hepatotoxic agents implicated in the literature as etiologic agents in cirrhosis of the liver.

(10) *Metabolic and Endocrine Factors.* Diabetes mellitus of mild degree was present in one patient. Connor<sup>4</sup> has commented on the rôle of diabetes mellitus in causing fatty infiltration of the liver, and the possible subsequent development of cirrhosis.

Hyperthyroidism was not present in any of the cases in this series, but impairment of liver function and cirrhosis of the liver have been reported in association with thyrotoxicosis.<sup>12</sup>

Gynecomastia (unilateral) was present in one patient but he had no other discernible endocrinopathic stigmata. Glass and his co-workers<sup>13</sup> reported eight cases of gynecomastia occurring in cirrhosis of the liver, and the foreign literature contains many references to this association. No other evidences of endocrinopathy were present in our series. Loss of body hair has been considered a feature of cirrhosis of the liver, but did not occur in any significant degree in our patients.

(11) *Diet.* Insufficient data were available with respect to the dietary habits of these patients to attempt to evaluate the importance of the dietary factor in this group.

However, recent experimental investigation has indicated the importance of adequate dietary protein in increasing resistance to hepatotoxic agents,

and the usually inadequate diet of the chronic alcohol addict is indubitably a significant factor predisposing to the development of cirrhosis.

(12) *Other Factors.* The rôle of malaria, enteric fevers, and tuberculosis in cirrhosis of the liver has been reviewed by Ratnoff and Patek.<sup>1</sup> With the exception that seven patients (10 per cent) of the series had had typhoid fever, these factors were not present to a significant degree in our patients.

No other significant etiologic factors were revealed by analysis of the series of cases presented here.

### CLINICAL FEATURES

The incidences of the various symptoms referable to cirrhosis are presented in table 3, where they are considered in the light of general incidence,

TABLE III  
Incidence of Complaints in Patients with Portal Cirrhosis

Complaint	Number of Patients		
	A	B	C
Ascites.....	39	31	22
Abdominal pain.....	34	8	12
Edema.....	34	9	13
Nausea and vomiting.....	31	1	5
Weakness.....	27	9	9
Jaundice.....	27	8	10
Weight loss.....	24	1	3
Gastrointestinal hemorrhage.....	15	4	3
Dyspnea.....	15	0	1
Constipation.....	8	0	0
Diarrhea.....	8	0	0
Epistaxis and/or ecchymosis.....	7	0	0
Rectal discomfort (hemorrhoids).....	2	1	1
Hematuria.....	1	0	0

Column A—General incidence

Column B—Incidence as presenting (or chief) complaint

Column C—Incidence as earliest complaints referable to cirrhosis

incidence as presenting complaint, and incidence as earliest complaint referable to cirrhosis. The incidence of positive physical findings is presented in table 4. Analysis of the clinical features in this fashion permits some interesting observations.

Several patients had more than one presenting complaint referable to cirrhosis (e.g., abdominal enlargement and jaundice). Three patients had no such complaints on admission, cirrhosis being an incidental finding at autopsy in two; the third patient entered the hospital for an elective hernioplasty, but examination revealed fever (of spiking character), marked hepatomegaly, severe anemia (2.5 million red blood cells per cu. mm.), and leukocytosis (25,000 white blood cells per cu. mm.), and a liver biopsy specimen showed well-advanced cirrhosis.

*Ascites.* Abdominal enlargement due to accumulation of ascitic fluid was the earliest complaint of 22 patients (31 per cent). It was the chief complaint at the time of admission in 31 cases, and an incidental complaint

TABLE IV  
Incidence of Physical Signs in Patients with Portal Cirrhosis

Sign	Number of Patients
Hepatomegaly.....	49
Ascites.....	44
Edema.....	42
Jaundice.....	37
Fever.....	35
Dilated superficial veins.....	29
Anemia.....	25
Malnutrition.....	24
Hemorrhoids.....	24
Splenomegaly.....	17
Nervous disturbances.....	15
Hydrothorax.....	7
Umbilical hernia.....	7
Inguinal hernia.....	5

in eight others, making a total of 39 patients (55 per cent) who *complained* of ascites. In addition, five patients were found to have free intraabdominal fluid on physical examination, bringing the total number of patients with ascites to 44 (63 per cent). Cirrhosis with ascites has been termed "de-compensated" cirrhosis.

The ascites of hepatic cirrhosis is probably due to the combined action of increased portal pressure<sup>14</sup> and decreased serum colloid osmotic pressure<sup>15</sup> secondary to the hypoalbuminemia commonly found in cirrhosis of the liver. Hypoproteinemia, primarily due to a lowered serum albumin content, with decrease or inversion of the A/G ratio, was a common finding in these patients, and frequently has been reported in cirrhosis of the liver.<sup>16, 17, 18, 19</sup>

Ascites was present in association with jaundice in 28 patients. Both jaundice and ascites have been considered ominous prognostic signs. In 18 patients who died in the hospital the duration of life from the onset of ascites was known, and averaged 7.5 months, with a range of 23 days to 38½ months. That ascites is not necessarily a fatal omen is indicated by the wide range, plus the fact that we have had under observation a patient whose initial complaint was ascites which developed in February 1938 and has recurred and subsided intermittently since that date; this patient is at present in a latent phase clinically. The observations of Fleming and Snell<sup>2</sup> on the treatment of portal cirrhosis with ascites also indicate that a more hopeful outlook is possible than has been entertained heretofore.

*Abdominal Pain.* Thirty-four patients (48 per cent) complained of abdominal pain during the course of their illness; in 12 patients, it was the earliest difficulty noted; and in eight patients it was the presenting complaint. The pain was usually a dull persistent aching sensation in the abdomen, particularly in the epigastrium, aggravated by the ingestion of food, and not relieved by the usual antacid medications and carminatives. In most cases, the pain could be attributed to the displacement and compression of the hollow viscera by hepatomegaly and ascites, or to functional gastrointestinal disturbances resulting from the impairment of the portal circulation. Fre-

quently, flatulence and "gas cramps" presented premonitory signs of the development of ascites. In nine patients abdominal pain was present without ascites; in three of these patients there was roentgenographic evidence of a duodenal ulcer; and a fourth patient had evidence of impaired cholecystic function as gauged by the dye excretion test. The remaining five patients without ascites were chronic alcohol addicts, and the pain may have been due, partially at least, to digestive disturbances secondary to the alcoholism. One patient with ascites and abdominal pain was found at autopsy to have chronic cholecystitis with cholelithiasis and a gastric ulcer. The frequency of coincidence of peptic ulcer or gall-bladder disease with cirrhosis of the liver has been discussed by Ratnoff and Patek.<sup>1</sup>

*Edema.* Edema of the lower extremities was noted by 34 patients, but was evident on physical examination in 42 (59 per cent). It was the earliest symptom in 13 patients, and the presenting complaint of nine patients. The edema involved the scrotum and lower abdominal wall in four patients, but there were no instances of edema of the face or upper extremities.

The most widely accepted explanation of the occurrence of edema in hepatic cirrhosis is that it is due either to (1) increased venous pressure in the lower extremities as a result of increased intraabdominal pressure (ascites), or (2) coexistent congestive failure. However, edema was present in the absence of ascites in nine patients in this series, in only two of whom were there evidences of congestive heart failure. The edema is, therefore, probably due primarily to hypoproteinemia,<sup>16</sup> with increased venous pressure as a significant factor only in those cases with massive ascites.

*Enlargement of the Liver and Spleen.* A palpable liver was found in 49 patients (70 per cent) and was the most common physical finding in this series. The average weight of the liver in the patients examined post-mortem was 2207 gm., the weight varying from 915 gm. to 4420 gm. As has already been noted, fatty infiltration was evident microscopically in eight of 21 livers examined. Although fatty infiltration may be responsible for hepatomegaly in many cases, it was not always found in the enlarged livers, and, vice versa, excessive fat was occasionally demonstrable in relatively small livers. Analyses of the fat and protein content of several livers from this series have been reported in connection with another study.<sup>20</sup>

The spleen was palpable in 17 patients (24 per cent) in this series, primarily as a result of congestion secondary to impaired portal circulation. Fibrosis of the spleen was evident on microscopic examination in five cases. The weight of the spleen in the patients examined post mortem averaged 395 gm. and varied from 150 gm. to 800 gm.

*Jaundice.* Jaundice was noted by 27 patients (38 per cent), being the earliest manifestation of cirrhosis in 10 patients, and the presenting complaint of eight. Physical examination revealed icterus in an additional 10 patients, bringing the total of jaundiced patients to 37 (52 per cent). Of 44 patients in whom the icteric index was determined, 28 had values of 10 units or higher, and 15 had values of 30 units or higher. Pruritus was a fre-



quent accompaniment of the higher degrees of jaundice, but clay-colored stools were rarely noted. Jaundice was present without ascites in 11 patients.

The presence of jaundice has been interpreted as an indication of activity of the disease process.<sup>1</sup> That jaundice is a sign of an advanced stage of the disease is indicated by the fact that the average duration of life after the onset of jaundice in the patients of this series who died in the hospital was 8.7 months, and that 63 per cent of the patients who died in the hospital were jaundiced. However, the jaundice may be intermittent, or may clear entirely. Jaundice was present in 17 (40 per cent) of the 42 patients who improved sufficiently to warrant discharge from the hospital, and the jaundice subsided before they were discharged.

*Weight Loss.* Loss of weight was one of the complaints of 24 patients (34 per cent), constituting the presenting complaint of one patient, and the earliest manifestation noted in three. Malnutrition was evident on physical examination in 24 patients, but these were not in all instances patients who complained of weight loss. The frequency of weight loss is difficult to evaluate since the accumulation of ascitic fluid or the development of edema may mask the wasting of flesh which occurs.

Emaciation, protuberant abdomen, sunken cheeks and temporal hollows, scleral icterus, a sallow complexion and facial telangiectasia constitute a characteristic clinical picture, and the diagnosis of hepatic cirrhosis may frequently be suspected from observation alone.

*Fever.* Temperature elevation for which the cause was not apparent was present in 35 cases (49 per cent). The fever was usually low-grade and of intermittent character and possibly reflected active inflammatory and degenerative processes in the liver parenchyma.

*Gastrointestinal Disturbances.* Abdominal pain, nausea, vomiting, and disturbances of bowel motility were the commonest evidences of disturbed gastrointestinal function. Abdominal pain has already been discussed. Nausea and vomiting occurred in 31 patients (44 per cent), constituting the earliest complaints of five patients, but the presenting complaints of only one. Eight patients complained of persistent constipation, and an equal number were distressed by diarrhea.

The occurrence of these difficulties is readily understandable when the abdominal contents are compressed by ascitic fluid. However, in 15 patients with gastrointestinal disturbances, ascites was absent and the dysfunctions were probably due to the impairment of the portal circulation.

*Gastrointestinal Hemorrhage.* Hematemesis occurred in 15 patients (21 per cent) and was the presenting complaint of four patients, in three of whom it was also the earliest manifestation of cirrhosis. Melena was noted terminally in two other patients. Despite the difficulty of demonstrating bleeding points at autopsy examination, it is believed that the hematemesis occurring in cirrhosis is due almost always to rupture of esophageal varices, although in one patient in this series gastric varices were evident at post-mortem examination.

Hematemesis, although an alarming occurrence, is not necessarily a fatal one, since seven of the 15 patients with hematemesis were among the group that improved and were discharged from the hospital. In eight patients the occurrence of gastrointestinal hemorrhage was followed by the gradual development of coma ending in death. Elevation of the blood non-protein nitrogen was observed after hemorrhage into the intestinal tract in three instances.

*Dyspnea.* Fifteen patients (21 per cent) complained of dyspnea; in four cases the dyspnea was attributable to congestive heart failure. In six other cases limitation of diaphragmatic excursion by ascites was considered responsible for the shortness of breath. In two patients accumulation of pleural fluid explained the dyspnea. In three instances, no ascites, hydrothorax, or congestive failure was found, and the etiology of the dyspnea here is not clear. Snell<sup>21</sup> observed reduction in the oxygen saturation of arterial blood in patients with chronic hepatic disease, and Darling<sup>22</sup> found that in six of 34 patients with cirrhosis slight degrees of arterial oxygen unsaturation were present which could not be explained by pulmonary disease. Possibly the unexplained dyspnea in the three instances noted above may be related to changes in properties of hemoglobin.

*Weakness.* Ready fatigability and weakness were specific complaints in 27 cases (38 per cent). It was the earliest difficulty noted by nine patients, and the presenting complaint of nine patients. However, some degree of weakness was probably present in a much greater number of cases than is evident from these figures. As might be anticipated, weakness and weight loss were commonly associated, but in most instances the weakness antedated the loss of weight.

*Hemorrhoids.* Rectal discomfort, dyschesia, or bleeding due to hemorrhoids were noted by only two patients. In one case, hemorrhoids were the presenting complaint; in the other, the hemorrhoids were the earliest difficulty noted. Physical examination, however, revealed dilated and protruding hemorrhoidal veins in 24 patients (34 per cent).

The occurrence of hemorrhoids in hepatic cirrhosis probably reflects the development of collateral circulation to aid the impaired portal drainage, although hemorrhoids are a relatively frequent finding in these age groups. That increased intra-abdominal pressure due to ascites may cause stasis in the hemorrhoidal veins is suggested by the fact that 18 of the 24 patients with hemorrhoids had ascites.

*Umbilical and Inguinal Hernias.* An umbilical hernia was found in seven patients (10 per cent). Each of these patients had massive ascites, and the hernia was undoubtedly due to the mechanical effects of the increased intra-abdominal pressure.

Inguinal hernias were observed in five patients (7 per cent), four of whom had ascites, and probably the same mechanism is partially responsible, although inguinal hernias are fairly common in patients of these age groups.

*Dilated Superficial Veins.* Prominence of the veins of the anterior ab-

dominal wall was evident in 29 patients (41 per cent) and reflected the development of collateral channels between the portal and systemic circulations.

*Hematuria.* Hematuria occurred in one case in this series and was attributed to rupture of a urethral varix. Libman, in discussing Christian's paper,<sup>23</sup> mentions rupture of distended vesical veins as a cause of hematuria occurring in cirrhosis of the liver.

*Bleeding Tendencies.* Epistaxis, purpura, ecchymosis, or bleeding from the gums occurred in seven patients (10 per cent), generally in association with clinically severe stages of the disease. In this series, hemorrhagic tendencies (exclusive of gastrointestinal hemorrhages) were observed only in jaundiced patients. The hemorrhagic phenomena exhibited by patients with cirrhosis of the liver are considered due to the hypoprothrombinemia which results from the inability of the damaged liver to manufacture prothrombin, even in the presence of vitamin K.

It has been suggested that mucosal angiomata may explain certain instances of bleeding.<sup>1</sup> The vascular "spider" associated with cirrhosis of the liver has been adequately described by Patek and co-workers.<sup>24</sup>

*Hydrothorax.* Accumulation of fluid in the pleural cavities occurred in seven patients (10 per cent). In six patients the effusion was evident on clinical or roentgenologic examination, while in the seventh it was found at autopsy examination. The effusion was bilateral in two patients, and unilateral in five (involving the left pleural cavity in two, and the right in three). All patients with pleural effusion also had ascites, and none of these presented evidence of cardiac disease. In two patients, the hydrothorax dominated the clinical picture and required frequent thoracenteses. In one instance, the pleural fluid was grossly bloody.

The mechanism underlying the development of hydrothorax in cirrhosis of the liver is not clear. Mallory<sup>25</sup> believes that in many cases there is a fairly free passage of fluid through the diaphragm, and in one of our patients thoracentesis usually resulted in an obvious decrease in the degree of ascites; the autopsy examination in this case disclosed no gross evidence of abnormality of the diaphragm. Increased capillary permeability has been advocated as an explanation for the hydrothorax occurring in cirrhosis, but Smirk<sup>26</sup> failed to find increased capillary permeability in cirrhosis. Decreased colloidal osmotic pressure, and mechanical interference with pulmonary circulation due to ascites have also been suggested as causes of hydrothorax in the absence of tuberculosis or renal or cardiac dysfunction.

Bloody pleural effusion occurring in cirrhosis of the liver has been reported previously by Christian,<sup>23</sup> who mentions other similar cases. The blood in the pleural fluid might be due to the bleeding tendencies of patients with cirrhosis.

*Nervous Disturbances.* The development of nervous disturbances progressing from restlessness to delirium and coma ending in death occurred in 15 patients (21 per cent), exclusive of the cases in which coma developed after massive hemorrhage. Coma has long been recognized as a frequent

manner of exodus of patient with cirrhosis, and transient paralyses and abnormal reflexes have been observed in such comatose patients. Because of the similarity of the neurologic findings to those of alcoholic encephalopathy, it has been suggested that the neurological changes might be due to a biochemical disorganization of the enzyme systems necessary for carbohydrate metabolism.<sup>27</sup>

In six of the 15 patients dying in coma, the development of stupor progressing to coma followed within a few hours the administration of morphine sulfate in dosage of 1/6 to 1/4 grain, and apparently was precipitated by the opiate (administered for pain or other indications). Mallory<sup>28</sup> mentioned that patients with cirrhosis may develop fatal coma after a single dose of morphine. Morphine is probably detoxified by conjugation with glucuronic acid in the liver,<sup>29, 30</sup> and it seems logical to assume that the cirrhotic liver may be unable to combine the glucuronic acid with the morphine, permitting the passage of free morphine, which may be more active pharmacologically than bound morphine (although this latter supposition is as yet unproved). However, it must be mentioned that in several other patients with cirrhosis, morphine had been administered intermittently frequently for the treatment of gastrointestinal hemorrhage or other indications, without apparent injurious effects. The effect of morphine in the causation of coma is not absolutely clear, but it seems wise to interdict the use of opiates in cirrhosis when less potent drugs may serve similar purposes.

*Changes in Blood Count.* A red blood count of less than four million cells per cu. mm., or a hemoglobin of less than 80 per cent or both, was found in 25 (53 per cent) of 47 patients for whom data were available. The color index was greater than one in 14 instances, and less than one in 11 instances.

The white blood cell count was above 10,000 cells per cu. mm. in 14 of 53 patients (26 per cent); in 10 of these 14 patients no cause for the leukocytosis was apparent, other than the cirrhosis of the liver. The differential counts were not unusual.

The erythrocyte sedimentation rate was determined in 30 patients and was increased beyond 20 mm. in an hour in 19 instances (63 per cent). The elevation of the sedimentation rate probably reflects inflammatory changes in hepatic parenchyma, and possibly alterations in plasma proteins.

*Elevation of the Blood Non-Protein Nitrogen.* Discussion of changes in blood chemistry and tests of liver function is beyond the scope of this paper, but it is of interest to note that the blood non-protein nitrogen was determined in 36 patients, and was elevated to 45 mg. per 100 c.c. or higher in seven instances (10 per cent). Jaundice was present in every patient with azotemia; in three instances, the elevation of the non-protein nitrogen was associated with hemorrhage into the gastrointestinal tract. Five of the seven patients with azotemia in this series died. Meyer and co-workers<sup>31</sup> have called attention to the significance of elevation of the non-protein nitrogen in jaundiced patients as a prognostic indication.

*Cause of Death.* In the 29 patients who died in the hospital, the average

duration of life from the development of the initial complaint referable to cirrhosis to the time of death was 11 months, and varied from two weeks to three years. In 15 patients, death was due to progressive "hepatic insufficiency," a vague nondescript term implying progressive failure of liver function and the gradual development of coma ending in death. Eight patients died from massive gastrointestinal hemorrhage. Four patients died of intercurrent infection (two of pneumonia, one of peritonitis, and one of streptococcal meningitis). In two cases the cause of death was uncertain.

### SUMMARY

1. The case histories of 71 patients with portal cirrhosis were reviewed with particular reference to etiologic factors and clinical findings.
2. The etiologic significance of age, alcoholism, and syphilis is found to be in accordance with previously accepted conceptions.
3. Fever, leukocytosis, and elevated sedimentation rate were found in a significant number of patients, and probably represent active inflammatory changes in the liver.
4. The possible relationship of the administration of morphine to the development of hepatic coma is discussed briefly.

### BIBLIOGRAPHY

1. RATNOFF, O. D., and PATEK, A. J., Jr.: The natural history of Laennec's cirrhosis of the liver—an analysis of 386 cases, *Medicine*, 1942, xxi, 207-268.
2. FLEMING, R. G., and SNELL, A. M.: Portal cirrhosis with ascites—an analysis of 200 cases with special reference to prognosis and treatment, *Am. Jr. Digest. Dis.*, 1942, ix, 115-120.
3. JOLLIFFE, N., and JELLINEK, E. M.: Vitamin deficiencies and liver cirrhosis in alcoholism. Part VII—Cirrhosis of the liver, *Quart. Jr. Studies on Alcohol*, 1941, ii, 544-583.
4. CONNOR, C. L.: Fatty infiltration of the liver and the development of cirrhosis in diabetes and chronic alcoholism, *Am. Jr. Path.*, 1938, xiv, 347-364.
5. CONNOR, C. L.: The etiology and pathogenesis of alcoholic cirrhosis of the liver, *Jr. Am. Med. Assoc.*, 1939, cxii, 387-390.
6. FRAME, E. G.: Lipotropic substances, *Yale Jr. Biol. and Med.*, 1942, xiv, 229-255.
7. SCHUMACHER, G. A.: Causative factors in the production of Laennec's cirrhosis with special reference to syphilis, *Am. Jr. Med. Sci.*, 1937, cxciv, 693-700.
8. BALDRIDGE, C. W.: The relationship between antisiphilitic treatment and toxic cirrhosis, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 685-690.
9. KATZIN, H. M., WALTER, J. V., and BLUMGART, H. L.: "Cardiac cirrhosis" of the liver—a clinical and pathologic study, *Arch. Int. Med.*, 1939, lxiv, 457-470.
10. BLOOMFIELD, A. L.: The natural history of chronic hepatitis (cirrhosis of the liver), *Am. Jr. Med. Sci.*, 1938, cxcv, 429-444.
11. MOON, V. H.: Histogenesis of atrophic cirrhosis, *Arch. Path.*, 1932, xiii, 691-706.
12. SHAFFER, J. M.: Diseases of the liver in hyperthyroidism, *Arch. Path.*, 1940, xxix, 20-30.
13. GLASS, S. J., EDMONDSON, H. A., and SOLL, S. N.: Sex hormone changes associated with liver disease, *Endocrinology*, 1940, xxvii, 749-752.
14. MCINDOE, A. H.: Vascular lesions of portal cirrhosis, *Arch. Path.*, 1928, v, 23-42.
15. BUTT, H. R., SNELL, A. M., and KEYS, A.: Plasma protein in hepatic disease, *Arch. Int. Med.*, 1939, lxiii, 143-155.

16. MYERS, W. K., and KEEFER, C. S.: Relation of plasma proteins to ascites and edema in cirrhosis of the liver, *Arch. Int. Med.*, 1935, *lv*, 349-359.
17. POST, J., and PATEK, A. J.: Serum proteins in cirrhosis of the liver, *Arch. Int. Med.*, 1942, *lxi*, 67-82.
18. ISRAEL, H. L., and REINHOLD, J. G.: Detection of cirrhosis and other diseases of the liver by laboratory tests, *Jr. Lab. and Clin. Med.*, 1938, *xxiii*, 588-596.
19. FOLEY, E. F., KEETAN, R. W., KENDRICK, A. B., and DARLING, D.: Alterations in serum protein as an index of hepatic failure, *Arch. Int. Med.*, 1937, *lx*, 64-76.
20. FAGIN, I. D., SAHYUN, M., and PAGEL, R. W.: Cirrhosis of the liver—the lipotropic action of parenterally administered amino acids, *Jr. Lab. and Clin. Med.*, 1943, *xxviii*, 987-993.
21. SNELL, A. M.: The effects of chronic disease of the liver on the composition and physico-chemical properties of blood: changes in the serum proteins; reduction in oxygen saturation of the arterial blood, *ANN. INT. MED.*, 1935, *ix*, 690-711.
22. DARLING, R. C.: Arterial oxygen saturation in cirrhosis of the liver, *ANN. INT. MED.*, 1940, *xiv*, 898-902.
23. CHRISTIAN, H. A.: Bloody pleural fluid, an unusual complication of cirrhosis of the liver, *Trans. Assoc. Am. Phys.*, 1937, *lii*, 167-170.
24. PATEK, A. J., JR., POST, J., and VICTOR, J. C.: Vascular "spider" associated with cirrhosis of the liver, *Am. Jr. Med. Sci.*, 1940, *cc*, 341-347.
25. MALLORY, T. B.: Discussion—case records of the Massachusetts General Hosp., Case No. 26441, *New England Jr. Med.*, 1940, *ccxxiii*, 731-734.
26. SMIRK, F. H.: Capillary permeability in cirrhosis with hypoproteinemia, *Clin. Sci.*, 1935, *ii*, 57-66.
27. SNELL, A. M.: Changing conceptions of portal cirrhosis, *Pennsylvania Med. Jr.*, 1942, *xlvi*, 337-344.
28. MALLORY, T. B.: Discussion, case records of the Massachusetts General Hospital, Case No. 26152, *New England Jr. Med.*, 1940, *ccxxii*, 643-646.
29. OBERST, F. W.: Relationship of the chemical structure of morphine derivatives to their urinary excretion in free and bound forms, *Jr. Pharmacol. and Exper. Therap.*, 1941, *lxxiii*, 401-404.
30. OBERST, F. W.: Studies on the fate of morphine, *Jr. Pharmacol. and Exper. Therap.*, 1942, *lxxiv*, 37-41.
31. MEYER, K. A., POPPER, H., and STEIGMANN, F.: Significance of rise of non-protein nitrogen in medical and surgical jaundice, *Jr. Am. Med. Assoc.*, 1941, *cxvii*, 847-850.

## SOME NOTES ON THE TRANSMISSION OF HEART MURMURS \*

By SAMUEL A. LEVINE, M.D., F.A.C.P., and WILLIAM B. LIKOFF, M.D.,  
*Boston, Massachusetts*

DESPITE the great antiquity of the practice of auscultation of the heart, it is surprising how little is known concerning the exact mechanism, production, and propagation of heart murmurs. Most of the information upon which prevailing medical teaching rests is derived from bedside observation correlated with postmortem findings. Little careful experimentation, either in man or animals, has been undertaken. Many simple questions concerning murmurs remain unanswered. Even trained experts in cardiology find great difficulty in explaining the mechanism of systolic murmurs, or in appraising their significance. This has been brought to our attention in a striking fashion during the present war when decisions have to be made concerning fitness for military duty of thousands of young men in whom the only abnormality is a systolic murmur. As examples of limitation of our knowledge one might mention several simple propositions. It would appear that with a small orifice such as is present in interventricular septal defect, or with a slight degree of mitral regurgitation, the resultant murmur (other things being the same) should be louder than if the lesion were larger. No definite proof of this observation appears to have been presented. When a systolic murmur accompanies a high degree of aortic stenosis, is the origin of the murmur in the blood itself, then transmitted to the neighboring structures, or does the sound originate in the wall of the aorta that is set in vibration, or possibly in the valve leaflets themselves? Similarly, when the mitral valve is involved, do the chordae tendineae, the papillary muscles, or the cardiac musculature itself play any rôle in the production of murmurs? It is obvious that the point of maximum audibility would be quite different if the murmur were made by the movement of the aortic valve cusps than if it were produced in the wall of the aorta. The reason that the systolic murmur in coarctation of the aorta is audible not only over the anterior chest, but in the interscapular region is that its point of production is deep in the middle of the chest, and it is transmitted in both directions. Does the gradual accentuation of a murmur, as a patient progresses from a moribund state to one of compensation, result from an increased vigor of muscular contraction, or to a decrease in dilatation of the heart and adjoining vessels? When a murmur has been produced, what is the mechanism of its transmission? Is it altogether propagated with the blood stream, and how important a factor is possible transmission through neighboring structures? Furthermore,

\* Received for publication June 4, 1943.

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston.

what makes one murmur audible over a large area, and another remain localized over a small area? Does the pitch, entirely apart from the intensity, play a rôle in the propagation of the murmur?

One factor, not sufficiently appreciated, that must have a bearing upon the production of murmurs is the velocity of blood flow. It is reasonable to assume that when fluid moves from one chamber into another through a constriction, if the caliber of the tube suddenly becomes narrowed or widened, the speed with which this movement takes place must affect the intensity of the resultant vibration or murmur. It was previously commented on<sup>1</sup> that many clinical conditions, such as hyperthyroidism, fever, anemia, excitement, and exercise, all associated with an increase in velocity of blood flow, frequently are accompanied by a systolic murmur. May not this same mechanism be involved in many other conditions where the measurement of the velocity of blood flow as customarily determined is normal? After all, it is not the speed of movement of blood from *arm* to *tongue* that would have any bearing on the production of murmurs, but rather the velocity of blood flow from one chamber of the heart to another, or from the ventricles through the aorta or pulmonary artery. An illustration in point is the situation that is present with a high degree of aortic stenosis. Here the total minute output of blood, the heart rate, and the velocity of blood flow, as measured from arm to tongue, may be perfectly normal, and yet the blood must go through an extremely narrow aortic orifice. The only possible explanation for this anomalous situation is that the speed of flow from left ventricle into the aorta must be terrific. This is supported by finding a firm, huge left ventricle as a rule in such cases of aortic stenosis. Such a ventricle must be expelling blood with great force. The appearance of the presystolic murmur of mitral stenosis after effort, previously inaudible at rest, is another instance in which the production of a murmur is determined by speed of blood flow. It is a common experience that the presystolic murmur of mitral stenosis is more readily heard with the patient lying in the left lateral position, and the diastolic murmur of aortic insufficiency with the patient sitting upright. Is this due to a closer proximity to the chest wall of the tissues producing the murmur, or to an increase in the velocity of blood flow through the respective valves in these positions? The complete disappearance or absence of the diastolic murmur in some cases of advanced mitral stenosis may well be due to the reverse of the mechanism discussed above. When the left auricle is markedly dilated, especially if fibrillation is present, and there is considerable weakening of the heart, even if the mitral valve is greatly stenosed blood flow from auricle to ventricle must be very sluggish. Furthermore, residual blood is present in the chambers of such hearts in large quantities. On postmortem examination cardiac chambers often are found to contain a half liter of blood or more. Inasmuch as only about 50 c.c. of blood are propelled with each systole, it is evident that blood is delivered into cavities that are already quite full. What effect does this residual blood have upon the production and propagation of murmurs?



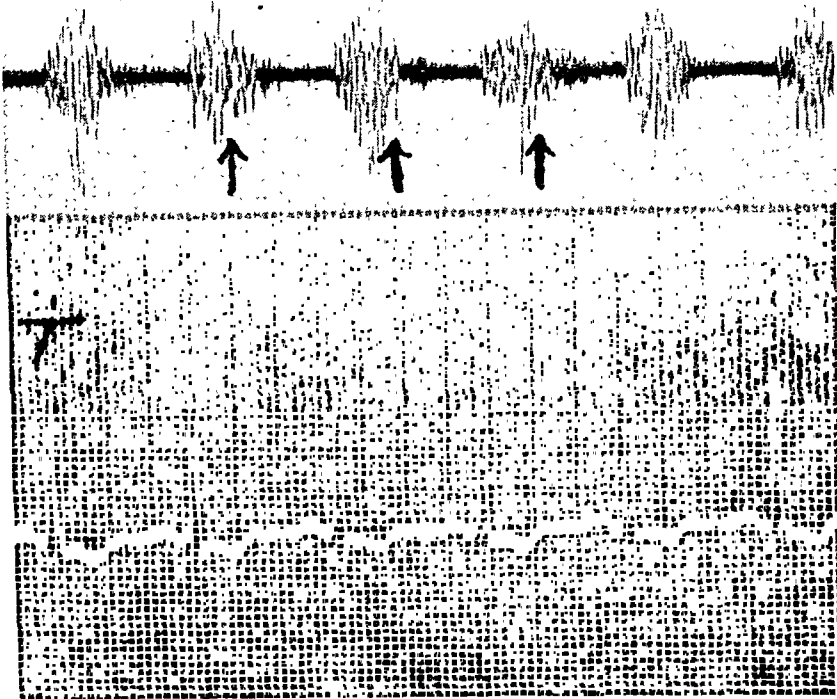
The entire subject of extracardiac murmurs is also very perplexing. When slight systolic murmurs are heard in patients with a thin chest wall, particularly when the antero-posterior diameter of the chest is small, can they be due to a purely mechanical contact or rubbing motion between the heart or great vessels and the chest? Furthermore, the movements of the lungs back and forth between heart and anterior chest wall may not only produce phasic cardio-respiratory murmurs, but can decrease and increase the intensity of endocardial murmurs. It, therefore, would seem fallacious to teach that a murmur that disappears or decreases strikingly with deep inspiration is necessarily unimportant or extra-cardiac.

In the interpretation of a murmur one is concerned with its location, its time in cardiac cycle, its character, and its intensity. Although the exact character of the murmur may at times be helpful, as illustrated by the continuous machinery-like noise of arterio-venous fistula, we believe that in appraising a systolic murmur the exact intensity is most important. We have advocated<sup>2</sup> grading intensity of murmurs from 1 to 6, 1 being the faintest that can be heard, and 6 being loud enough to be audible with the stethoscope just removed from the chest wall. As a matter of experience it has been found that systolic murmurs of grade 3 intensity or louder occur only when there is some form of heart disease, endocardial or myocardial, or in those diseases, like marked anemia, which occasionally are accompanied by murmurs. On the other hand, murmurs of grade 1 intensity (and occasionally even of grade 2 intensity) are frequently observed where most careful examination fails to reveal any organic disease of the heart or any other important organ. The difficulty is that a loud grade 5 murmur of aortic stenosis, for example, does not attain this intensity over night, and must have gone through the stage when it was only grade 1. It is during these early stages of the development of murmurs that our diagnostic criteria are very inadequate.

It is clear from the above that many important questions concerning cardiac murmurs remain unanswered. The purpose of this study is to present some data concerning one or two of the above points. First, we will present evidence to show that murmurs are transmitted through bone, and that very likely the transmission through blood stream is unimportant, and, secondly, that the disappearance or marked decrease in intensity of a murmur with deep inspiration does not mean that it is "functional."

For many years it has been our growing conviction that the transmission of murmurs is mainly, if not entirely, a function of intensity, i.e. loud murmurs are widely distributed and faint ones are not. The current teaching that aortic systolic murmurs are transmitted to the neck and mitral systolic murmurs to the axilla has the connotation that murmurs are transmitted with the blood stream. From a purely physical point of view it seems illogical to assume that sound is transmitted in the direction of and with the blood stream, for the speed of transmission of sound through liquid is much faster than the velocity of blood flow. Therefore, the transmission that

A Aortic Area



B. Olecranon Process

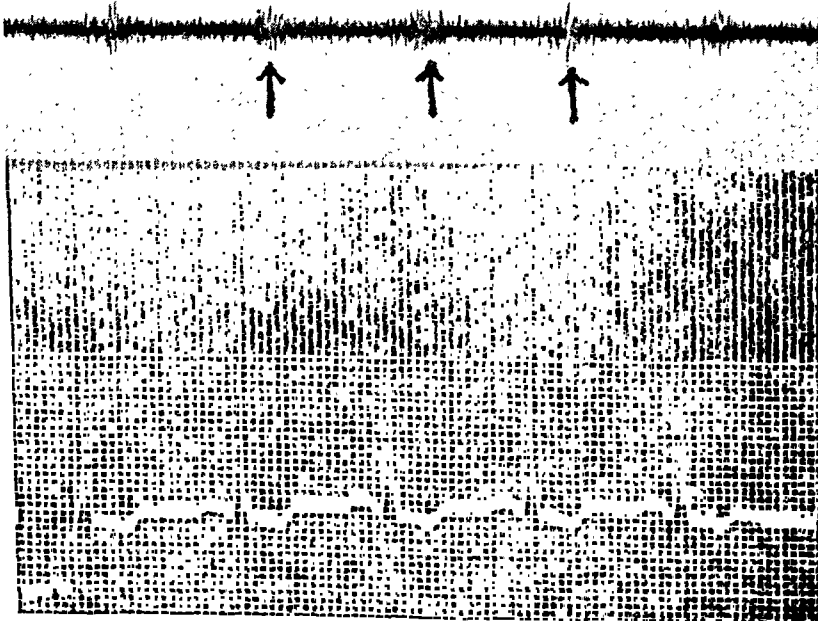


FIG. 1, A and B. Simultaneous phonocardiograms and electrocardiograms on a woman, aged 38, with marked aortic stenosis. Record A was obtained from the aortic area, and shows marked systolic murmur (arrows). Record B was from the right olecranon process and shows definite systolic murmur coming slightly later than the aortic murmur (arrows).

C Olecranon Process  
B.P. Cuff Inflated.

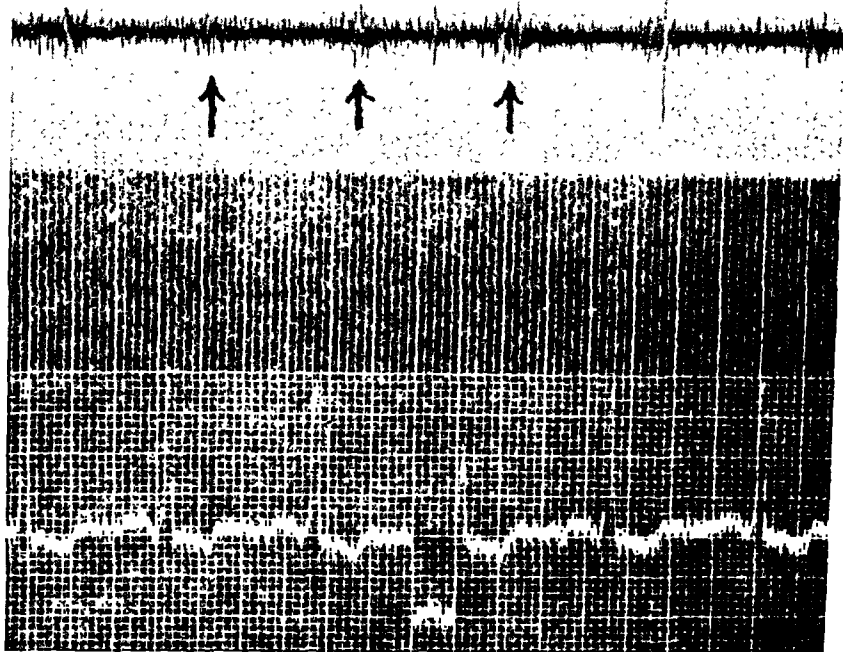


FIG. 1, C. Record C was also from the right elbow, but with the blood pressure cuff inflated to 220 mm. (patient's pressure was 160/80). Note persistence of systolic murmur (arrows). (Cambridge Instrument Co. machine.)

does take place occurs "in" and not "with" the blood stream and would be distributed equally both against and in the direction of the blood flow. It has even been thought that a systolic murmur heard over the aortic area and also over the carotid artery was much more likely due to aortic stenosis than if it were not heard in the neck. Likewise, an apical systolic murmur that was well heard in the axilla would have a greater value in indicating mitral insufficiency than if it were not transmitted in this fashion. The contention that we wish to maintain is that a loud aortic systolic murmur will be heard in the neck because it is near the neck, and a loud apical murmur will be audible in the axilla for the same reason. It should follow that a very loud pulmonary systolic murmur, or any grade 5 or 6 murmur, ought to be audible in the carotid region. That this is true will be seen below. In general, we feel that a murmur is transmitted in all directions from the point of maximum intensity, and that once the sound strikes bone it is best transmitted through contiguous bony structures. At first this idea was merely a suspicion, but, when, for many years, loud systolic murmurs were detected over the olecranon process with the ordinary bell stethoscope, it became more of a conviction. Finally, it might have been maintained that a systolic murmur present over the bony process of the elbow was still transmitted from a neighboring blood vessel. This possibility was eliminated when the sound

remained audible even after pressure, above the level of the systolic blood pressure of the patient, was maintained proximal to the olecranon process.

Figure 1 was obtained in the case of a woman, aged 38, with marked aortic stenosis having a loud, grade 6, aortic systolic murmur. Record A was taken from the aortic area and shows a loud systolic murmur. Record B was obtained with the microphone over the olecranon process of the right

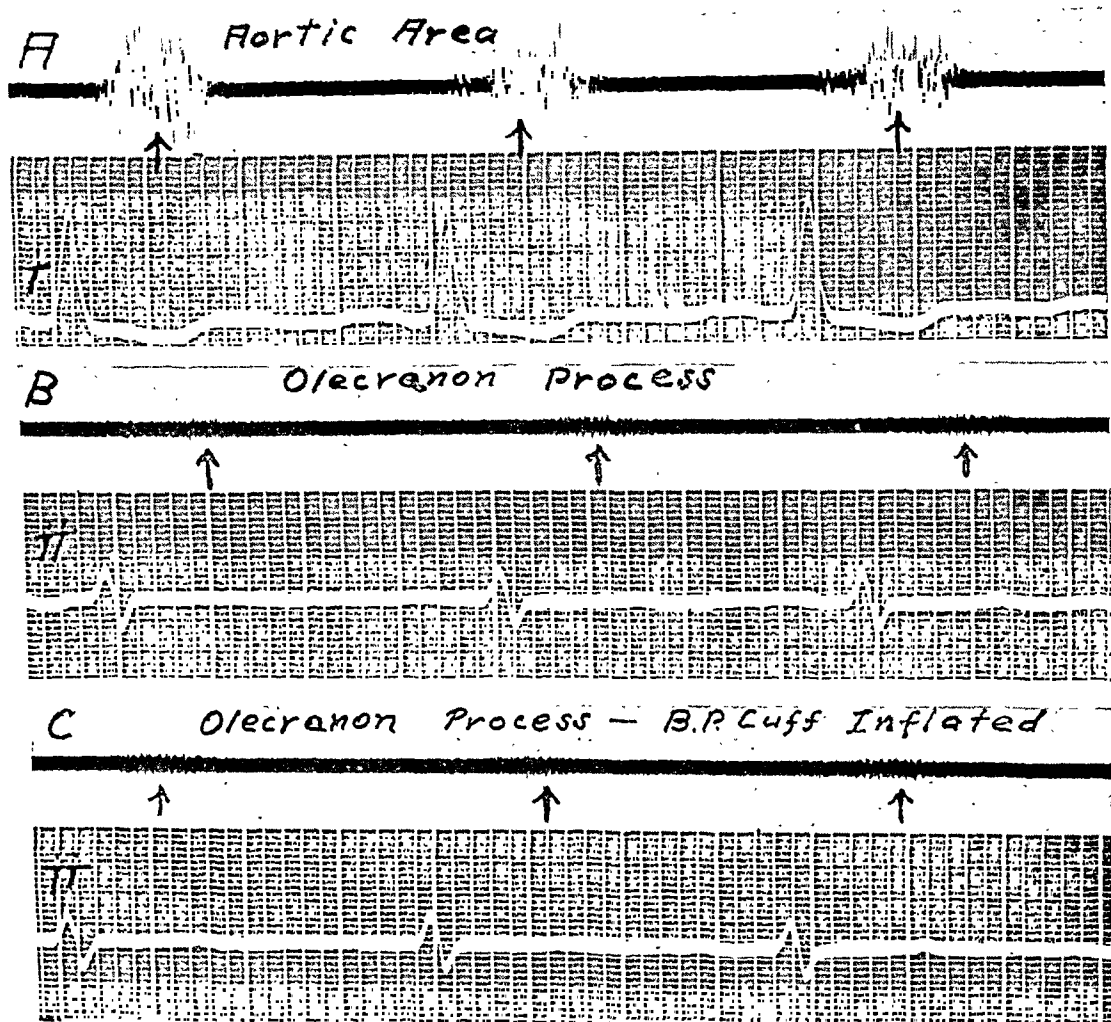
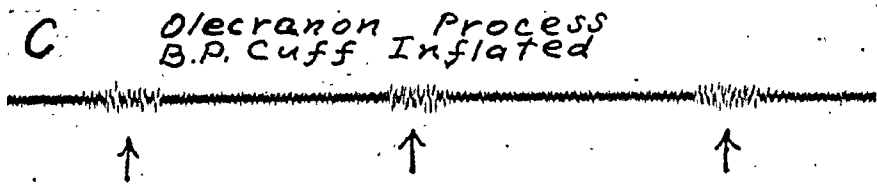
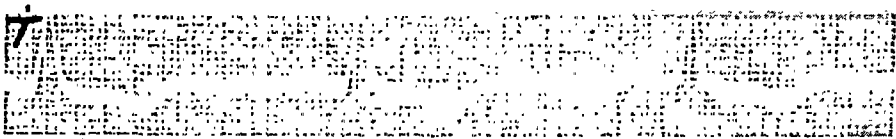


FIG. 2. Similar data on the same patient as in figure 1, but obtained six months later. (Sanborn Co. machine.)

elbow and shows definite vibrations late in systole. Record C, also obtained from the olecranon process, shows that the murmur persists after the pressure in the blood pressure cuff was raised well above the patient's systolic level. Figure 2 shows similar findings obtained on the same patient six months later with a different apparatus.\* With careful auscultation, using the

\* We wish to thank M. B. Rappaport, E.E., of the Sanborn Co., for some advice in this work.



ordinary stethoscope, these faint, clearly detectable, systolic murmurs have been heard over the elbow in many different cases. Another instance is very clearly illustrated in figure 3, obtained from a woman aged 44 with marked aortic stenosis.

In these two cases systolic murmurs were transmitted very widely through bone. In the following instance (figure 4) a very loud, musical, grade 6, aortic diastolic murmur was present in a man about 50 years of age with syphilitic aortic insufficiency. It was suspected that this patient ruptured an aortic cusp, for, after a sudden, violent strain, he first became aware of a noise in his chest. Here the blood flow producing the murmur was taking place from aorta into the left ventricle during diastole. Despite this, the murmur was readily heard, widely distributed and easily detected at the top of the skull and over the olecranon process.

If the transmission of a murmur primarily depends upon its intensity, then it should follow that a murmur that is very loud over the base of the heart, produced in the pulmonary valve or in some other area, such as a defect in the interventricular septum, ought to be detectable in the region of the carotid artery, just as occurs in cases of aortic stenosis. Figure 5 shows that this supposition is true. This patient was a young man of 23, known to have a heart murmur since birth, showing definite evidence of an interventricular septal defect (Roger's disease). He had a grade 6 systolic murmur best heard over the mid-precordium, and there was right bundle branch block in the electrocardiogram. The murmur was very loud over the pulmonary area, as shown in the first several beats of record A (figure 5). The transmission of the murmur to the neck is clearly indicated in record B. A similar mechanism is illustrated in figure 6. This woman, aged 29, had classical signs of tetralogy of Fallot. There was a grade 5 systolic murmur in the pulmonary area due to pulmonary stenosis (figure 6, record A). This murmur was also clearly audible over the carotid artery (record B). It must be appreciated that in the first of these two cases the flow of blood producing the murmur was from left ventricle to right ventricle through the septal defect, and in the second instance was from right ventricle through a stenosed pulmonary valve into the pulmonary artery. The presence of the murmur in the carotid artery, therefore, can not be accounted for by the flow of blood through the aorta, but must be transmitted from its origin within the right ventricle on the one hand, and the pulmonary artery on the other.

In evaluation of a systolic murmur it is common practice to have the patient exercise, or to observe the effect of breathing on the murmur. In a previous communication<sup>2</sup> it was clearly established that most normal adults develop a grade 1 to grade 2 apical systolic murmur directly after a brisk

---

FIG. 3. Simultaneous phonocardiograms and electrocardiograms on a woman 44 years of age with marked aortic stenosis. Record A shows coarse systolic murmur (arrows) at aortic area. Record B shows systolic murmur detected at olecranon process (arrows), and record C shows the same murmur (arrows) with blood pressure cuff inflated to 220 mm. (patient's blood pressure was 158/60).

effort. It is likewise true that a slight systolic murmur can become accentuated after such effort. Figure 7 was obtained from a 24 year old medical student with no evidence whatever of cardiac disease. Record A shows the absence of any murmur at the apex of the heart. Record B was taken within 30 seconds after a period of brisk exercise and depicts the fine systolic murmur heard at the apex and classified as grade 1. No diagnostic conclusion, therefore, can be drawn from the detection of a systolic murmur that is produced by exercise.

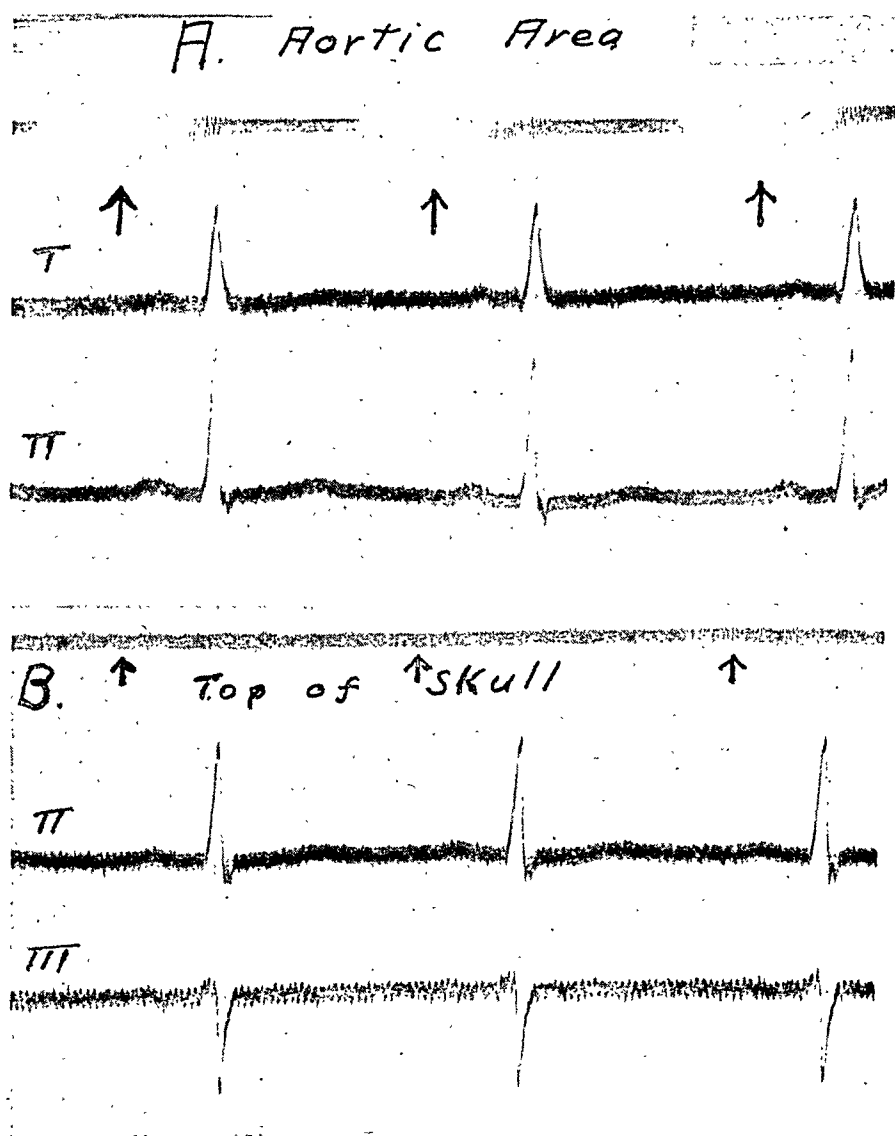


FIG. 4, A and B. Simultaneous phonocardiograms and electrocardiograms on a man about 50 years of age with syphilitic aortic insufficiency with possible ruptured aortic valve. There was a grade 6 musical aortic diastolic murmur. Record A shows fine diastolic murmur (arrows) in aortic area. Record B shows faint diastolic murmur (arrows) obtained from top of skull.

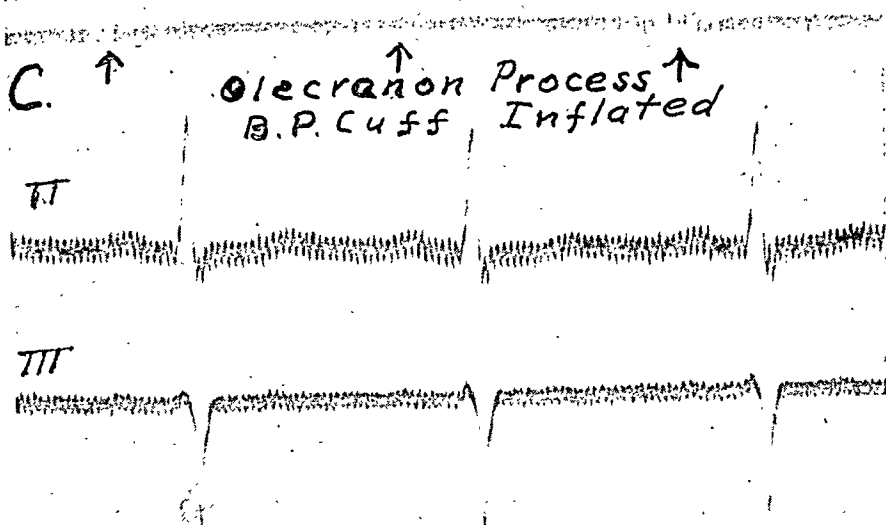


FIG. 4, C. Record C shows moderate diastolic murmur (arrows) from olecranon process with blood pressure cuff inflated to 220 mm. (patient's blood pressure was 140/60). (Courtesy of Drs. Henry H. Haft and Jane Sands Robb of Syracuse, N. Y.)

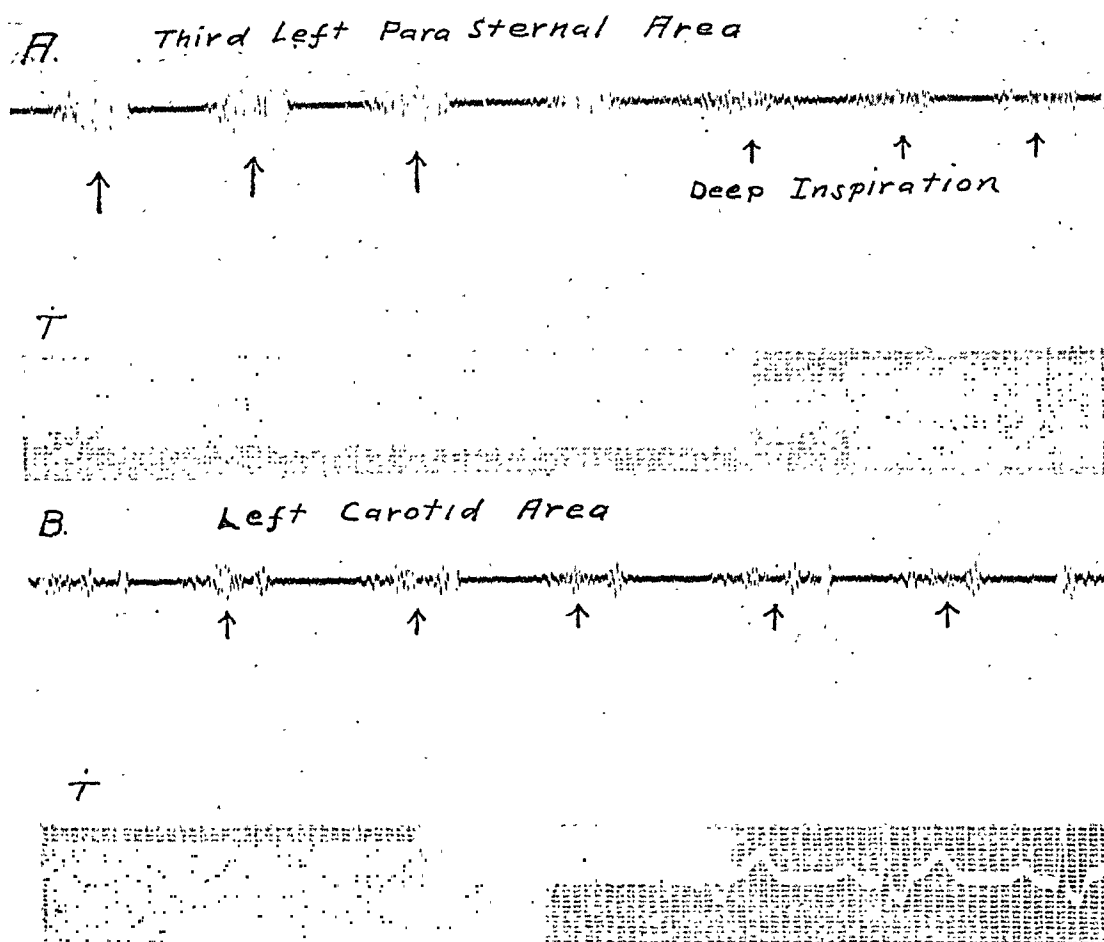
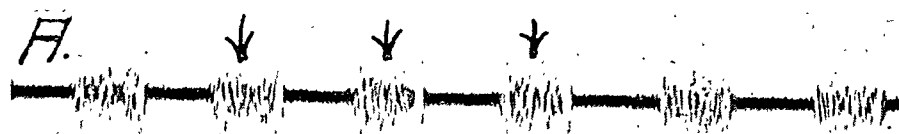
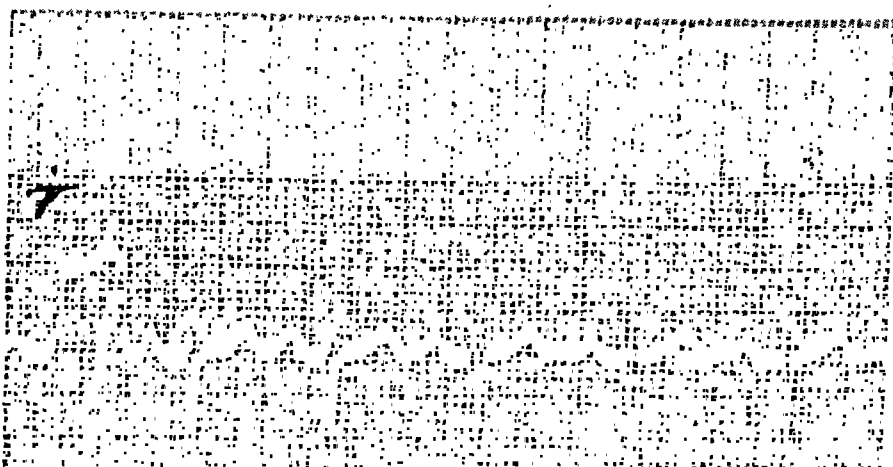


FIG. 5. Simultaneous phonocardiograms and electrocardiograms on a young man of 23 with interventricular septal defect. Record A was taken from the third left parasternal area and shows a loud systolic murmur (arrows) which, after several cycles, becomes faint on taking a deep inspiration. Record B, obtained from the left carotid area, shows definite, moderate systolic murmur (arrows).





Third Left Para Sternal Area



Left Carotid Area.

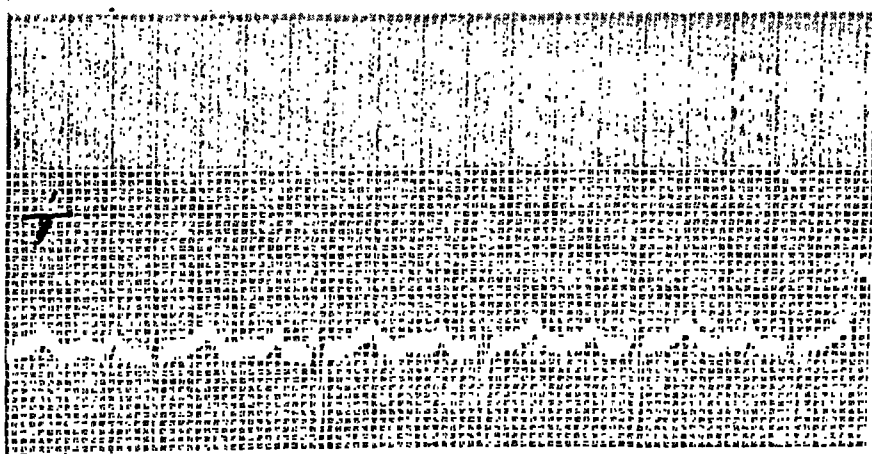
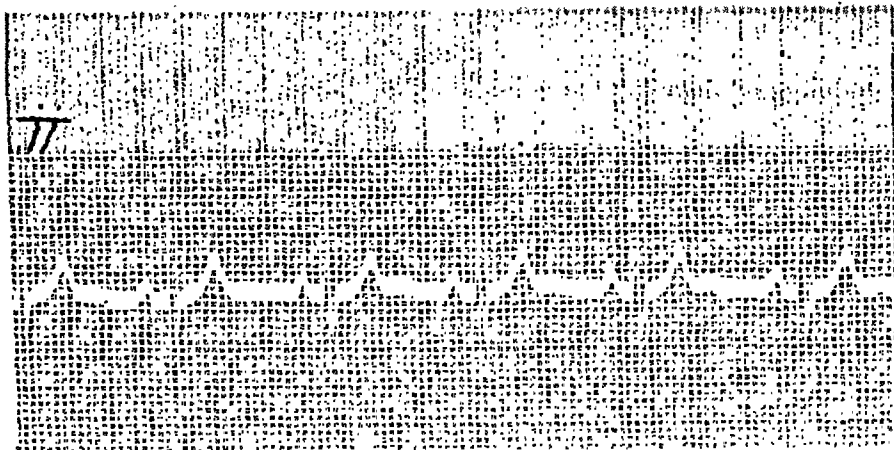


FIG. 6. Simultaneous phonocardiograms and electrocardiograms on a woman, aged 29, with tetralogy of Fallot. Record A, from third left parasternal area, shows loud systolic murmur (arrows). Record B, from upper left carotid area, shows definite, moderate systolic murmur (arrows).

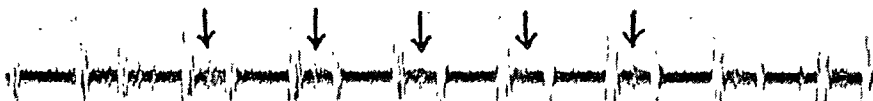
*A.*



*Apex  
Before Exercise*



*B.*



*Apex  
After BRISK Exercise*

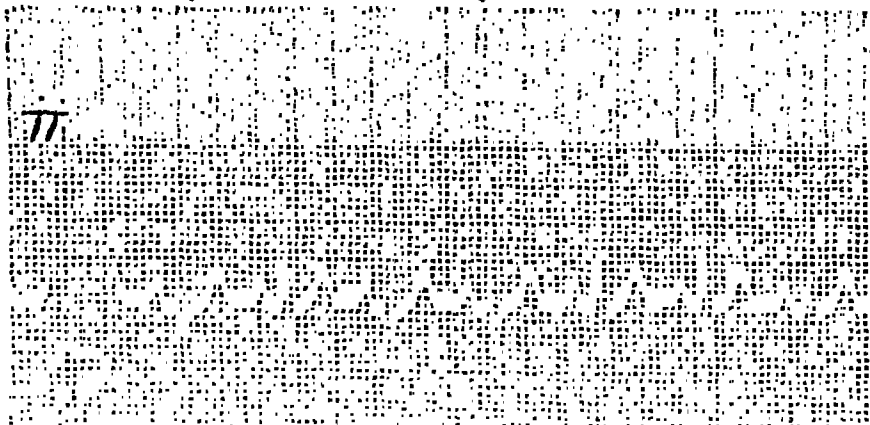


FIG. 7. Simultaneous phonocardiograms and electrocardiograms on a medical student of 24 with no heart disease. Record A, taken at the apex, fails to show any murmur. Record B, taken within 30 seconds after a period of brisk exercise, shows a fine systolic murmur (arrows) which was clearly heard at the apex and classified grade 1.

Even the relation between deep breathing and the systolic murmur is no simple matter. Any faint murmur, systolic or diastolic, pathologic or functional, may diminish or disappear on taking a deep breath. This is what one might expect, for all heart sounds can become more distant as a greater amount of lung tissue intervenes between the heart and chest wall. This is well illustrated in figures 5 and 8. The loud basal systolic murmur of pulmonary stenosis decreased markedly on deep inspiration (figure 5), and an aortic diastolic murmur, in a case of aortic insufficiency, actually disappeared on deep inspiration (figure 8). It is clear, therefore, that intracardiac or

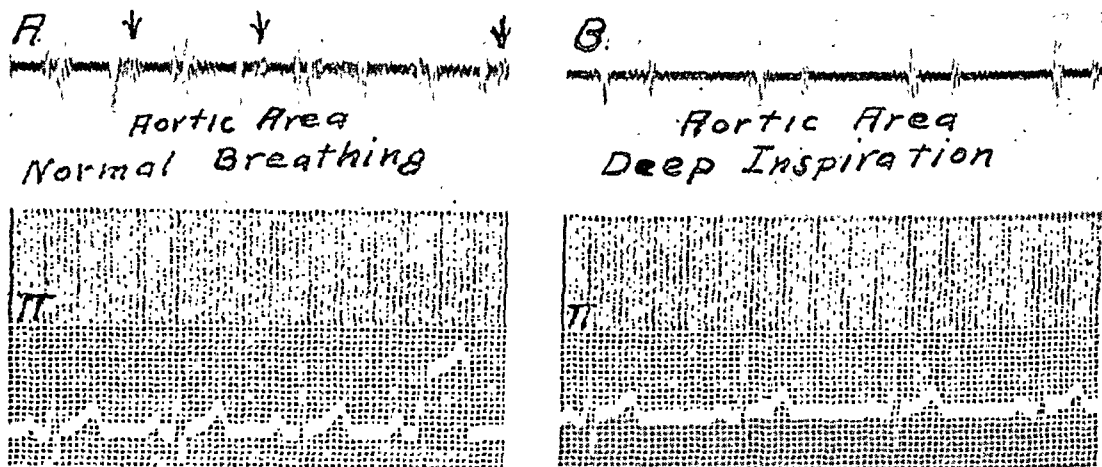


FIG. 8. Simultaneous phonocardiograms and electrocardiograms on a young man of 26 with aortic insufficiency. Record A shows an aortic diastolic murmur (arrows) with patient breathing normally that entirely disappeared on taking a deep inspiration (record B).

endocardial murmurs can vary in intensity with respiration. There are, however, purely extra-cardiac or cardio-respiratory murmurs heard at the apex and especially at the pulmonary area that vary with the respiratory cycle. In some instances such systolic murmurs come and go rhythmically with respirations, increasing with expiration and decreasing with inspiration. We have a suspicion that some cardio-respiratory systolic murmurs are only present at certain phases of inspiration, as if the cushion of lung receives the systolic impact with each beat. In other instances, especially in thin-chested individuals, the pulmonary systolic murmur may be present only with a deep expiration. May this not be due to the actual impact of the pulmonary artery against the chest wall? It is obvious that the simple question of the relation of heart murmurs to respiration needs further investigation.

#### SUMMARY AND CONCLUSIONS

1. Numerous simple questions concerning the production and propagation of murmurs remain unanswered.
2. We believe that the velocity of blood flow through the cardiac chambers and great vessels is one important factor in the production of murmurs and in determining their intensity.

3. Other factors, such as the amount of residual blood in cardiac chambers, the proximity of the heart and great vessels to the chest wall, and the respiratory cycle may influence the presence or absence of murmurs.

4. We believe that the gradation of systolic murmurs from 1 to 6 is important in attempting to estimate their significance, for those of grade 3 intensity, or louder, are never observed in normal individuals, whereas those of grade 1, and occasionally grade 2, are found where there is no evidence of cardiac or other disease.

5. The detection of murmurs over the olecranon process even with the blood pressure cuff inflated above the systolic pressure level, proves that murmurs are transmitted through bone.

6. The transmission of an aortic diastolic murmur to the skull, and of the systolic murmur of ventricular septal defect to the carotid area proves that murmurs are not propagated with the blood stream, for the blood flow in these circumstances is in the opposite direction.

7. Systolic murmurs after effort occur in normal individuals. The production or accentuation of such murmurs after exercise, therefore, can not be used as a diagnostic test.

8. There are several mechanisms involved when murmurs are influenced by respiration. All faint murmurs, organic or functional, may disappear with a deep inspiration. In some instances extracardiac systolic murmurs may be louder, and in others fainter, with a deep expiration.

9. The current teaching about propagation of murmurs needs revision.

10. These considerations are important in the examination of selectees for military service.

#### BIBLIOGRAPHY

1. LEVINE, S. A.: The systolic murmur: its clinical significance, *Jr. Am. Med. Assoc.*, 1933, ci, 436-438.
2. FREEMAN, A. R., and LEVINE, S. A.: The clinical significance of the systolic murmur: A study of 1000 consecutive non-cardiac cases, *ANN. INT. MED.*, 1933, vi, 1371-1385.

# CASE REPORTS

---

## PATENT DUCTUS ARTERIOSUS WITH PULMONARY VASCULAR SCLEROSIS AND CYANOSIS\*

By CARLETON B. CHAPMAN, M.D., and STANLEY L. ROBBINS, M.D.,  
*Boston, Massachusetts*

PATENT ductus arteriosus is a congenital cardiac lesion usually producing a shunt of blood from the aorta to the pulmonary artery. Cyanosis in the condition is rare, although a transient cyanosis may sometimes be seen following bouts of crying or coughing.<sup>1</sup> Maude Abbott states that the left ventricle is characteristically more enlarged than the right, but a recent report by Keys and Shapiro<sup>2</sup> indicates that the reverse may be true. Pulmonary vascular sclerosis and polycythemia are not components of the syndrome as usually described. The following case of patent ductus arteriosus is remarkable in that (a) there was cyanosis of at least five years' duration, (b) there was a striking degree of right ventricular hypertrophy, (c) pulmonary vascular sclerosis was advanced, and (d) secondary polycythemia was consistently found.

### CASE REPORT

A 37 year old married taxi driver was admitted to the Boston City Hospital on January 30, 1943 for the tenth time.

He stated that when 12 years old he had had an attack of rheumatic fever. He was accepted for life insurance at the age of 14 but was refused further insurance at the age of 26 because of a "heart murmur." In March, 1936, at the age of 30, he visited the Out Patient Department complaining of increasing dyspnea on exertion for one year. His heart was enlarged, the left border being 11.5 cm. from the midline in the fifth left interspace, and a low-pitched diastolic murmur was heard in the third and fourth left interspaces 4 cm. from the midline. The diagnosis at that time was rheumatic heart disease with mitral stenosis.

He was admitted to the hospital in December, 1938, complaining of breathlessness, cough and bloody sputum for one day. On physical examination the patient was very plethoric and cyanotic about the face and lips. Venous engorgement was absent. The AP diameter of the chest was slightly increased, and there were a few moist râles at the base of the left lung. The heart size and murmurs were the same as recorded two years previously. Neither the liver nor the spleen was felt. The blood pressure was 140 mm. Hg systolic and 95 mm. diastolic in the arms and in the legs. The urine contained small amounts of albumin. The hemoglobin varied between 21 and 25.7 grams per 100 c.c. blood (Sahli). The red cell count varied between 6 and 7 million per cu. mm. The white cells were within normal limits in number and types. The hematocrit varied between 60 and 74.5 per cent. Five sputum examinations were negative for tubercle bacilli. The venous pressure in the right arm was 6 cm. of

\* Received for publication July 23, 1943.

From the Thorndike Memorial Laboratory, the Second and Fourth (Harvard) Medical Services and the Mallory Institute, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

water. Arterial oxygen saturation was 75 per cent. An electrocardiogram showed right axis deviation. The discharge diagnoses were congenital heart disease with pulmonary insufficiency and patent interauricular septum.

Between the first entry in 1938 and the final entry in 1943, the patient was admitted eight times complaining variously of dyspnea on exertion, small hemoptyses and swollen, painful joints. The hemoglobin and red cell count were always in the neighborhood of 18 grams per 100 c.c. of blood (Sahli) and 8 million per cu. mm., respectively. Venesections were carried out approximately 20 times, 500 to 600 c.c. being removed each time with considerable symptomatic relief. A systolic murmur was regularly heard in the fourth left interspace, but the previously reported diastolic murmur was infrequently heard. Arterial oxygen saturation values during 1940 and 1941 varied between 89 and 94 per cent. Fluoroscopic and roentgenographic examinations at various times during this period demonstrated marked general enlargement of the heart and a prominent pulmonary conus. The right ventricle was considerably enlarged and hyperactive, whereas the left auricle appeared normal.

While a patient at the Peter Bent Brigham Hospital in 1942 the heart size and murmurs were found to be the same as originally noted, although the diastolic murmur was not heard by all observers. The effect of oxygen administration on arterial oxygen saturation was studied in Dr. C. Sidney Burwell's laboratory and the following results obtained:

Before oxygen administration .....	82 per cent saturated
After 30 minutes' exposure .....	100 per cent saturated
10 minutes after stopping oxygen .....	97 per cent saturated
Vital capacity .....	3.5 liters

Five days before the tenth and last admission to the Boston City Hospital, the patient noted pain on the dorsum of the left foot followed after 12 hours by hemoptysis and sharp pain in the left lower chest. The hemoptysis and chest pain did not recur, but the pain in the left foot continued, ultimately causing him to seek hospitalization.

On physical examination the temperature was 98.6° F., the pulse rate 90, and the respiratory rate 24. The blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. The plethoric, cyanotic appearance noted in 1938 was still present. There was no venous engorgement, and the lungs were entirely clear. The heart was enlarged 12 cm. to the left of the midsternal line and there was a rough apical systolic murmur. No diastolic murmur was heard. P2 was louder than A2. The liver was felt three fingers' breadth below the costal margin. Both great toes were red, cyanotic and tender to motion, but the temperature of the affected joints was normal. Dorsalis pedis and posterior tibial arterial pulsations were bilaterally palpable. The veins of the legs were not palpable, and there was no calf tenderness.

Significant laboratory data included a hemoglobin of 16.4 grams per 100 c.c. blood (Sahli), a red cell count of 7.6 million, and a white cell count of 6800 per cu. mm. All urine specimens contained rare red cells, granular casts and moderate amounts of albumin. An electrocardiogram showed marked right axis deviation.

On the second hospital day a venesection of 500 c.c. was performed. Later in the day it was decided, largely on the basis of the history, that the patient had a thrombosis of the veins of his leg, giving rise to pulmonary infarcts. Femoral ligations were advised by the surgical consultants and the operation was performed about 48 hours after admission. While in the operating room, the patient suddenly became very dyspneic and cyanotic. He responded to the administration of oxygen, caffeine and coramine but on return to the ward again became very dyspneic. Oxygen and various restoratives were given, but in spite of these measures he gradually became comatose and died 12 hours after the operation. Discharge diagnoses were congenital

heart disease with interauricular septal defect, secondary polycythemia and pulmonary infarcts.

*Postmortem Examination.* Externally the body was that of a normally developed, well-nourished adult male, appearing considerably older than his stated age of 37 years. There was a patchy cyanosis of the face, neck and shoulder girdle.



FIG. 1. View of the right side of the heart showing from below above, greatly thickened right ventricle, healed pulmonic endocarditis, dilated pulmonary artery with its main branches and widely patent ductus surrounded by many atheromatous plaques.

There were bilateral recent healing skin incisions over the femoral veins, each 10 cm. in length. There was only slight edema over the dorsum of the left foot. There was a slight precordial bulge but no clubbing of the fingers or toes.

The peritoneal cavity was without pathologic change. Pleural and pericardial cavities contained normal amounts of clear, serous fluid. The heart was enlarged,

weighing 680 grams, and anteriorly was composed almost completely of the right ventricle so that the left ventricle appeared to be an appendage to the preponderant right ventricle. The epicardium was essentially negative. The myocardium of



FIG. 2. Large artery showing in right lower field an asymmetrical internal atheroma with fibrous internal proliferation. Verhoeff. elastic tissue stain  $\times 40$ .

the right ventricle was greatly increased in thickness, varying from 1.8 to 2.2 cm., in striking contrast to the essentially normal left ventricle with a thickness of 1.4 cm. The right atrium was dilated and there was slight dilatation of the right ventricle.



The tricuspid and pulmonic valve rings were similarly dilated to 15.0 and 11.0 cm., respectively. The leaflets of all the valves, with the exception of the anterior cusp of the pulmonic valve, were thin, translucent and flexible with no evidence of atherosclerosis or fibrous thickening of intercommissural adhesions. The anterior leaflet of



FIG. 3. Medium-sized artery with fairly marked intimal atherosclerosis; thrombosis and recanalization of lumen. Verhoeff. elastic tissue stain  $\times 50$ .

the pulmonary valve presented at the mid-point of its base a heaped-up, irregular, mulberry-like calcific mass measuring 1.5 by 1.0 by 0.5 cm. These calcified vegetations were everywhere smooth and glistening and were completely covered with endothelium. They penetrated the leaflet and protruded within the sinus of Valsalva.

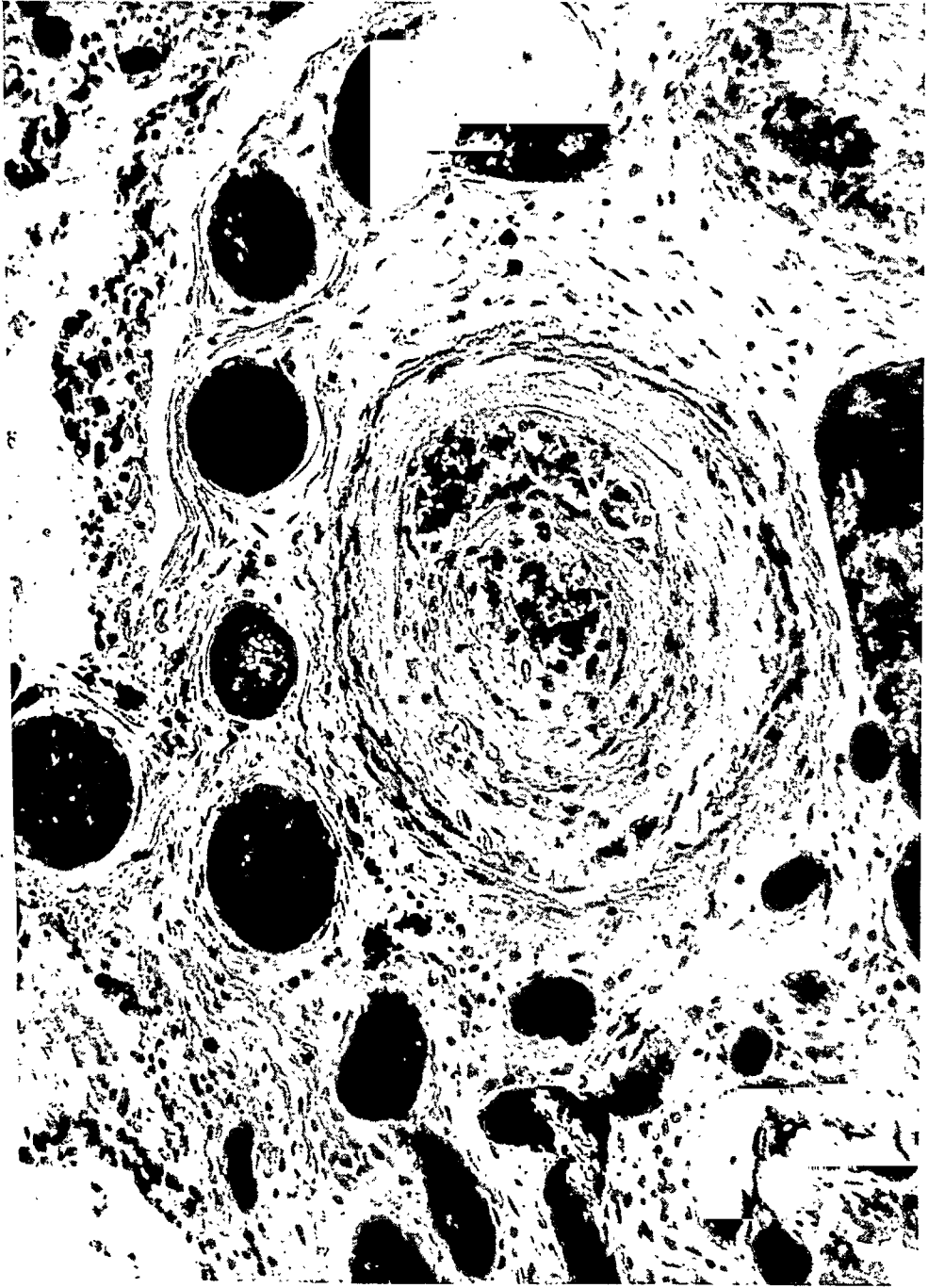


Fig. 4. Small artery of lung showing hyperplastic endarteritis with narrowing of lumen. Phloxine-methylene blue stain  $\times 150$ .

Attached to this basal mass and extending to the free margin of the valve cusp was a thin subendocardial calcific plaque which made the cusp stand out rigidly from the wall. The main pulmonary artery was moderately dilated to a maximum of 12 cm. in circumference. It contained a marked amount of calcific atherosclerosis. There was a widely patent ductus arteriosus 8 cm. distal to the pulmonary valve ring at



FIG. 5. Small artery showing marked thickening and tortuosity of elastica interna with a similar, but less dominant, change in the externa. Verhoeff. elastic tissue stain  $\times 500$ .

the point where the pulmonary artery is in direct apposition to the aorta. It was roughly circular in outline with a diameter of 1.2 cm. and its opening in the wall of the pulmonary artery was surrounded by a large calcification (figure 1). The ductus consisted of a simple opening connecting the lumina of the great vessels. No calci-

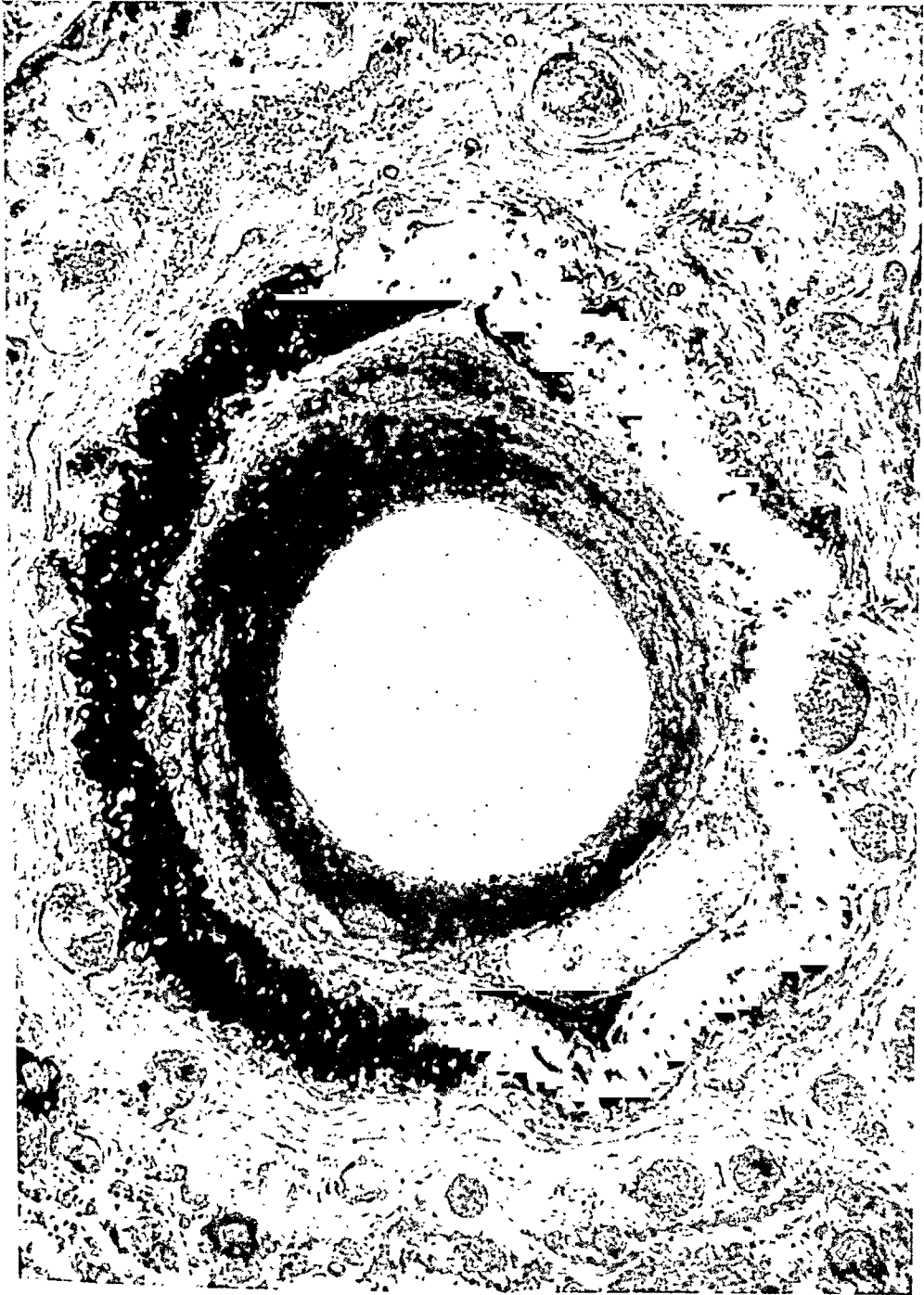


FIG. 6. Medium-sized artery showing destruction of a well-defined elastica interna, diffuse increase in elastic tissue within intima and media; thickening and re-duplication of elastica externa. Verhoeff. elastic tissue stain  $\times 200$ .

fied vegetations were seen about the margin of the ductus save for the described atherosclerosis.

The lungs were essentially negative grossly, each weighing 340 grams and containing no definite evidence of infarction or hemorrhage. The pulmonary arterial

tree, while containing no emboli, showed diffuse thickening of the walls of all the grossly visible vessels so that on cut section they protruded above the parenchymal surface in "pipe-stem" fashion. The spleen and liver were moderately enlarged. The two kidneys weighed 460 grams and except for the slight increase in their size and weight were grossly negative. The veins of the legs were explored down to the ankles and were entirely patent except at the points of operative ligature. The brain showed no pathologic change. The anatomical diagnoses were: (a) congenital heart disease, patent ductus arteriosus, healed pulmonic endocarditis, cor pulmonale (marked), (b) pulmonary atherosclerosis, (c) right-sided cardiac decompensation as evidenced by splenomegaly and hepatomegaly.

Microscopically, the only findings of interest were in the lungs, liver and kidneys. The lungs showed no microscopic evidence of recent infarction. The alveolar spaces were entirely clear except for a slight amount of amorphous, albuminous precipitate in the basal portion of both lower lobes. Of greatest interest were the arteries which showed in the larger branches thickening of the walls by far advanced intimal atherosclerosis, which in one vessel had led to thrombosis of the lumen with subsequent organization and recanalization (figures 2 and 3). The medium-sized elastic arteries and smaller muscular arteries showed relatively greater thickening of their walls so that in certain areas the lumina were diminished to fine capillary-like channels (figure 4). The increase in thickness was due to fibrous intimal proliferation. In addition to the above findings there was a remarkable increase in the elastic tissue content of all the arteries. This increase took a variety of forms. In some vessels it consisted in great thickening chiefly of the elastica interna with relatively little change in the externa. In other vessels, the externa appeared to have undergone reduplication and splitting with no apparent change in the interna (figures 5 and 6).

Throughout most vessels, a marked increase in the elastic fibrils could be demonstrated in the media and intima, often associated with complete destruction of a clearly defined elastica interna. No definite correlation could be drawn between the type of elastic tissue change found and the size of the vessel. Study of representative samples of systemic vessels in malignant hypertension and pulmonary vessels in mitral stenosis demonstrated no elastic tissue changes comparable with the above findings. Phosphotungstic acid-hematoxylin stains revealed no significant abnormality within the media or adventitia, except for a slight increase in perivascular fibrous tissue with dilatation of the vasa vasorum.

The smallest arteries and arterioles were normal, showing no evidence of hyperplastic or necrotizing arteriolitis. At the bases of both lower lobes the alveolar capillaries showed moderate dilatation with some reduplication and tortuosity of their courses. In the main, however, the alveolar walls were unlike those described by Parker and Weiss,<sup>8</sup> and presented only minimal intramural edema and fibrosis.

The liver showed marked acute hemorrhagic central necrosis of the lobules.

The kidneys were of interest in that the glomeruli presented increased cellularity due to endothelial proliferation with splitting of the basement membrane. The picture was considered to be consistent with a late stage of acute diffuse glomerulonephritis. No vascular changes were found elsewhere in the body. The heart presented no microscopic evidence of an earlier rheumatic involvement.

## DISCUSSION

In the light of the preceding pathologic data it seems possible to correlate to some extent the findings of patent ductus arteriosus, pulmonary vascular sclerosis, right ventricular hypertrophy, and cyanosis.

Normal blood pressures in the pulmonary arterial tree are considered by standard textbooks to approximate one-sixth of systemic blood pressure values.

Hence, in the usual case of patent ductus arteriosus, the shunt must be from left to right. In addition, Burwell and colleagues<sup>4</sup> have shown by animal and clinical experimentation that as much as 40 to 75 per cent of the total left ventricular output may pass through a patent ductus, depending upon the size of its lumen. Inasmuch as the patient under consideration had a widely patent ductus it seems reasonable to infer that large amounts of aortic blood were added to the pulmonary circulation. This increase in pulmonary blood volume must have created initially a slight pulmonary hypertension which became severe as a later result. The latter manifested itself in a fashion exactly analogous to systemic hypertension, namely by ventricular hypertrophy and vascular sclerosis; in this case by hypertrophy of the right ventricle and sclerosis of the pulmonary arterial tree. A similar thesis, namely that the vascular changes constitute a "physiopathologic response to pulmonary hypertension," has been suggested in connection with *primary* pulmonary vascular sclerosis by Brill and Krygier.<sup>5</sup> The vascular changes, as has been pointed out, are of the secondary type,<sup>6</sup> being prominent within the larger branches of the pulmonary artery and practically negligible within the smallest arteries and arterioles. The most common conditions producing elevated pulmonary pressures, e.g., left ventricular failure and mitral stenosis, place a strain initially on the pulmonary veins and capillaries. Since these portions of the pulmonary vascular system are highly distensible, effects of the increased pressure may be very late, and although capillary changes may be seen microscopically, there is usually little or no pulmonary arterial change, consisting, when present, of atherosclerosis in the larger vessels. In our case, however, the shunting of large amounts of arterial blood directly into the pulmonary artery produced pronounced pulmonary arterial changes with minimal capillary and venous changes.

The etiology of the cyanosis observed in the patient after 1938 is obscure. Three independent or combined possibilities present themselves:

- (1) Entrance of venous blood into the systemic circulation via the patent ductus arteriosus.
- (2) Peripheral venous stagnation.
- (3) Pulmonary vascular changes.

In regard to the first possibility, it seems unlikely that the pulmonary hypertension ever reached such levels as would create a right to left shunt except possibly as a terminal event. Relative to peripheral venous stagnation, it is noteworthy that there was never clearly defined clinical evidence of congestive failure. However, the pathologic findings of right ventricular hypertrophy and dilatation, and hemorrhagic necrosis of the liver indicate that some degree of right ventricular decompensation must have been present. In addition, "in a subject with an abnormally high blood count a degree of slowing of the peripheral blood flow which would be without effect upon a person possessing a normal hemoglobin content will result in cyanosis."<sup>7</sup> This is, of course, only an "appearance." Actually, the per cent of unsaturation for a given loss of oxygen will be less in polycythemia. That pulmonic factors were of some significance is supported by the oxygen saturation tests carried out in Dr. Burwell's laboratory, which indicated that exposure of the patient to 80 per cent oxygen raised the saturation of the arterial blood from 82 to 100 per cent. This result is inconsistent with the passage of venous blood directly into the arterial circulation and suggests that the passage

of oxygen from the alveoli to the red blood cells may have been impaired. On the basis of these data it was Dr. Burwell's opinion that while the patient was at rest there was no shunting of blood from right to left. He felt that the cyanosis was pulmonic in origin and suggested that a left to right shunt might impose a burden on the pulmonic circulation and result in a "progressive pulmonary abnormality." The relationship of pulmonary sclerosis to cyanosis is not clear. The sclerotic process involved the larger elements of the pulmonary arterial tree, and did not affect per se the alveoli or alveolar capillaries, the actual sites of oxygen transfer. Cyanosis was present in 17 per cent of the cases of secondary pulmonary vascular sclerosis collected by Brenner.<sup>6</sup> He doubted, however, that there was any relation between pulmonary vascular sclerosis and the production of cyanosis. The edema of the alveolar walls and tortuosity of the alveolar capillaries found in this case, however minimal, may have to some extent impaired oxygen diffusion across the alveolar membrane.

Complete absence of murmurs and murmurs which change from time to time have been reported in proved cases of patent ductus arteriosus. Keys and Shapiro<sup>2</sup> state that atypical and inconstant murmurs are particularly likely to occur in the final stages of failure. Presumably, with sufficient rise in pulmonary blood pressures, the left to right shunt may become diminished or abolished, thus producing changes in or even disappearance of murmurs.

The findings of healed pulmonic endocarditis and acute glomerulonephritis were considered incidental in this case. They in no way contributed to the course which the case took beyond serving as additional reasons for the development of systolic murmurs on the one hand and urinary findings of albumin, casts and red cells on the other. The widely differing ages of these lesions renders unlikely any causal relationship between the two and places them merely in the category of coincidental findings.

The immediate cause of death in this patient was probably cardiac failure, as was suggested not only by his clinical course but also by the signs at postmortem examination of severe hemorrhagic central necrosis, marked cor pulmonale, and right ventricular dilatation.

### SUMMARY

An unusual case of patent ductus arteriosus is presented which, clinically, showed prolonged cyanosis, an inconsistent pulmonic diastolic murmur, and polycythemia. At postmortem examination a widely patent ductus arteriosus was demonstrated, together with marked right ventricular hypertrophy and sclerosis of the pulmonary arterial tree. The last two postmortem findings were considered to be manifestations of pulmonic hypertension. We are unable to offer an adequate explanation for the cyanosis. However, the evidence at hand is against the direct passage of blood from the venous to the arterial circulation.

### BIBLIOGRAPHY

1. ABBOTT, M. E.: Atlas of congenital cardiac disease, Am. Heart Assoc., 1936, New York.
2. KEYS, A., and SHAPIRO, M. J.: Patency of the ductus arteriosus in adults, Am. Heart Jr., 1943, xxv, 158.
3. PARKER, F., JR., and WEISS, S.: The nature and significance of the structural changes in the lungs in mitral stenosis, Am. Jr. Path., 1936, xii, 573.

4. EPPINGER, E. C., BURWELL, C. S., and GROSS, R. E.: The effects of the patent ductus arteriosus on the circulation, *Jr. Clin. Invest.*, 1941, xx, 127.
5. BRILL, I. C., and KRYGIER, J. J.: Primary pulmonary vascular sclerosis, *Arch. Int. Med.*, 1941, lxxviii, 560.
6. BRENNER, O.: Pathology of the vessels of the pulmonary circulation, part III, *Arch. Int. Med.*, 1935, lv, 724.
7. BEST, C. H., and TAYLOR, N. B.: The physiological basis of medical practice, Third Ed., 1943, Williams and Wilkins, Baltimore, p. 621.

## FATAL AGRANULOCYTOSIS FOLLOWING THE INTRA-PERITONEAL IMPLANTATION OF SULFANILAMIDE CRYSTALS \*

By WILLIAM R. ARROWSMITH,† M.D., BARBARA BINKLEY, M.D., and CARL V. MOORE, M.D., F.A.C.P., *St. Louis, Missouri*

COMPARATIVELY few severe toxic reactions have resulted from the local use of sulfonamide drugs, presumably because relatively small amounts are placed in the tissues and because excretion is prompt.<sup>1</sup> It has been demonstrated that with the dosages used in local application there is only temporary appearance of the drug in the blood.<sup>2, 3</sup> The few severe reactions which have been described relate chiefly to the production of hepatic damage. Watson and Spink<sup>4</sup> reported fatal hepatitis in two individuals who had received sulfanilamide by intra-peritoneal implantation, and Jackson and Coller<sup>5</sup> observed nine instances of jaundice in a group of 62 patients to whom sulfanilamide had been given in the same manner. The development of jaundice in these last nine patients cannot be attributed with certainty to the intra-peritoneal administration because additional sulfanilamide had been given orally as well. Recently there have appeared descriptions of cutaneous reactions which followed the topical use of sulfathiazole ointment.<sup>5, 6</sup> The present report describes a different type of toxic reaction, that of acute agranulocytosis which developed in a patient 17 days after five grams of crystalline sulfanilamide had been placed in his peritoneal cavity. Although agranulocytosis is one of the well recognized complications of sulfanilamide therapy,<sup>7-15</sup> its occurrence after the local use of this drug has not previously been described.

### CASE REPORT ‡

F. H., a white man 42 years of age, was admitted to the Barnes Hospital on February 29, 1940, with the history of having recently vomited small amounts of blood. He was known to have had a peptic ulcer for nine years. Roentgenologic examination of his gastrointestinal tract showed the presence of a duodenal ulcer and of pyloric obstruction. He was discharged from the hospital with instructions to adhere to an ulcer-diet and to take alkaline powders. During the next year he had no

\* Received for publication May 2, 1943.

From the Department of Internal Medicine and the Department of Pathology, Washington University Medical School, and from Barnes Hospital, St. Louis, Missouri.

† Research Fellow of the American College of Physicians at the time these observations were made; now 1st Lt. MC, AUS. This article was completed before the author entered military service.

‡ We are indebted to Dr. Glover H. Copher for permission to report this case.



symptoms, and roentgen-ray studies demonstrated less gastric retention than had been present in February, 1940. However, during the summer of 1941 the symptoms of ulcer recurred and he experienced several small hematemeses. Fluoroscopic re-examination of his stomach in February, 1942 showed a greater degree of gastric retention than had been noted the previous year. On February 26, 1942, he vomited large amounts of blood and was again admitted to the hospital.

At this time the patient appeared to be a well nourished man who was neither acutely ill nor uncomfortable. His blood pressure on admission was 120 mm. Hg systolic and 90 mm. Hg diastolic; there were no detectable manifestations of shock. The abdomen was not tender and no masses were felt. The remainder of the physical examination was not remarkable.

The Kahn test was negative. No abnormalities were noted on urinalysis. The non-protein nitrogen content of the blood was 25 mg. per hundred c.c. Guaiac tests for occult blood in the stools were strongly positive. Red blood cell counts varied between 3,370,000 and 4,620,000 per cu. mm., and hemoglobin values ranged from 9.5 to 13.5 gm. per 100 c.c. Other hematologic data are recorded in table 1.

TABLE I

Date	WBC	Differential Count						
		Eos.	Bas.	Myel.	Non-segmented Neutrophiles	Segmented Neutrophiles	Lym.	Mono.
1940								
2-29	9,300	0	0	0	10	63	23	4
1942								
2-26	3,850	0	1	0	2	56	34	7
3-26	2,700	0	0	0	26	42	20	8
3-27	4,650	0	0	0	25	52	18	3
3-30	2,550	0	0	0	0	2	96	2
4-1	400	0	0	0	0	6*	94*	0

\* Only 35 cells were found in a complete search of two coverslip preparations.

Transfusions were given and treatment was conservative during the first two weeks of this hospitalization period. However, because of gastric retention and continuing gastrointestinal bleeding, a laparotomy was performed on March 13 under nitrous oxide and ether anesthesia. Scar tissue was found to have completely encircled the first part of the duodenum, where an ulcer had perforated posteriorly into the pancreas. A partial gastrectomy, gastro-enterostomy and jejunojejunostomy were done. Because of presumed contamination of the peritoneal cavity, approximately five grams of sulfanilamide crystals were scattered along the suture lines and over the areas of resection.

Food was well tolerated after 72 hours. The patient's course was uneventful until the evening of his twelfth post-operative day when his temperature rose suddenly to 39.5° C. A fine erythematous rash was noted on his trunk. On the next day he was seen by a dermatologist, Dr. C. W. Lane, who wrote the following note: "The patient has a bright red color of the face, ears, and neck with slight edema of the ears. There is a punctiform erythema of the chest, abdomen and back and a morbilliform rash on the arms, forearms, legs and thighs. No pruritus or burning. No strawberry tongue and no pharyngitis. The color fades readily on pressure. . . ." Dr. Lane considered the skin lesion to be a drug rash and suggested that it had been caused by the sulfanilamide. No sulfanilamide could be detected chemically in blood samples taken on March 28 and March 30. The rash, however, became more intense;

by March 30 the entire skin surface showed a bright erythema, a few small red macular areas were noted on the buccal mucosa, the conjunctivae were intensely injected and severe photophobia was present.

On March 26 the white blood cell count was 2,700 per cu. mm.; there was a marked increase of non-segmented forms of neutrophilic leukocytes. Four days later the granulocytes had almost disappeared; they remained markedly decreased until the patient's death on April 1. The reticulocyte count on April 1 was only 0.2 per cent; the platelet count was 657,000 per cu. mm. Sternal bone marrow obtained by aspiration on April 1 was found to contain very few myeloid cells, a diminished number of nucleated red cells, apparently normal megakaryocytes, and an increased number of small lymphocytes and phagocytic clasmotocytes. The patient was given two additional transfusions. However, on April 1, 19 days after his operation, he developed evidences of bronchopneumonia and died the same evening.

During the 33 days of his final hospitalization period, this man had received, in addition to the sulfanilamide placed in his peritoneal cavity, the following drugs: nembutal .09 gm. at bed-time for five nights, February 26 to March 2; alkaline powders\* 1 gm. t.i.d. for 8 days, March 5 to March 13; phenobarbital .03 gm. t.i.d. for 8 days, March 5 to March 13; and morphine sulfate .015 gm. hypodermically four times during the first two days after the operation.

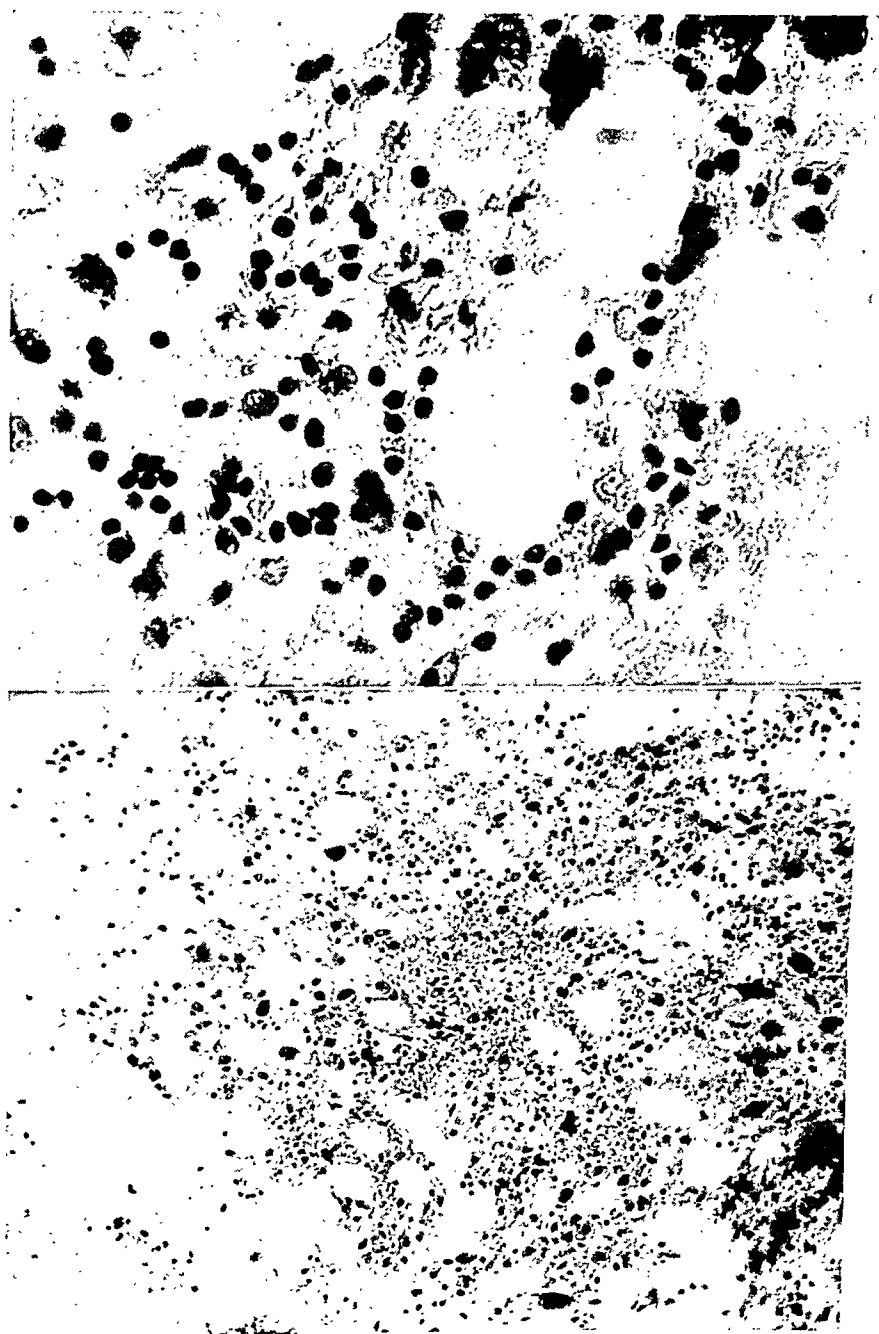
#### AUTOPSY REPORT

The autopsy was performed by Dr. Jane Erganian two hours post mortem. No abnormalities not recorded in the physical examination were noted on external examination. The peritoneal cavity contained about 800 c.c. of slightly cloudy yellow fluid. The peritoneum was hyperemic but was smooth and glistening. There were fibrous adhesions between the omentum, mesentery, and visceral peritoneum and the anterior parietal peritoneum. The wound of a partial gastrectomy with an anastomosis between the jejunum and stomach, and the two limbs of the jejunum at the gastrojejunostomy were partially healed. The proximal end of the duodenum was a blind pouch where it had been severed from the stomach (Polya operation). Each pleural cavity contained 200 c.c. of slightly cloudy yellow fluid. The lungs, particularly the lower lobes, were firm and red in color and a moderate amount of yellowish-red fluid could be expressed from the cut surfaces. The surfaces of the kidneys were slightly granular; there were small petechiae in the mucosa of the pelvis. The bone of the sternum and vertebrae was well calcified and there were numerous trabeculae. The bone marrow was yellow and translucent with foci of red, more cellular tissue. The heart, liver, spleen, pancreas, adrenals, urinary bladder, prostate, reproductive organs, and lymph nodes showed no significant gross abnormalities beyond those listed in the final pathologic diagnoses tabulated below.

Sections were taken for microscopic study from the sternal, costal, and vertebral bone marrow, and from all of the viscera. All sections of bone marrow showed marked hypoplasia of the myeloid elements, congestion, and hemorrhage (figure 1). The normal hemopoietic structure was partly replaced by fat cells and there were large areas of mucinous degeneration. Numerous normoblasts and megakaryocytes, both normal and necrotic, were present. Very few myelocytes and no mature granular leukocytes were noted in the sections. A few large cells resembling reticulum cells were observed.

The pulmonary alveoli were filled with large clumps of bacteria, red blood cells, fibrin, and occasional mononuclear cells. No polymorphonuclear leukocytes were present. There were necrosis and slight hemorrhage about the central veins of the liver. Numerous large phagocytic cells were present but no polymorphonuclear cells.

\* Composed of calcium carbonate 40 parts, sodium bicarbonate 30 parts, bismuth subcarbonate 20 parts, magnesium oxide 10 parts.



(a)  $\times 135$

(b)  $\times 570$

FIG. 1. Bone marrow from vertebra.

The sinusoids of the spleen were greatly dilated and the lining cells protruded into the lumen. Few cells were present in the pulp with only occasional large macrophages and numerous red blood cells. The Malpighian bodies were inconspicuous. Sections of the kidneys showed slight thickening of the basement membranes and of the capsules of the glomeruli. No other pathological lesions were noted in the kidneys. Sections from the heart, pancreas, adrenals, from the wound of the gastroenterostomy, and the inverted stump of the duodenum showed no significant pathological changes.

The final pathological diagnoses were: hypoplasia of the myeloid elements of the bone marrow; central necrosis of the liver; ascites (800 c.c.); petechiae of the mucosa of the sclerae and renal pelvises; bronchopneumonia of all lobes of the lungs; hydrothorax (200 c.c.); hydropericardium (100 c.c.); lipoidosis of the pulmonary, coronary, and splenic arteries; arteriosclerosis of the aorta, slight; sclerosis of the anterior leaflet of the mitral valve; arteriolar nephrosclerosis, slight; fenestrations of the cusps of the aortic valve; hemangiomas of the liver; focal hyperplasia of the renal tubules.

### DISCUSSION

Acute agranulocytosis developed in this man 17 days after five grams of sulfanilamide had been placed in his peritoneal cavity, and death occurred two days later. Changes in his peripheral blood were characteristic of acute agranulocytosis: profound leukopenia with a selective decrease in granulocytes, a normal platelet count, and no disturbance in red cells. His anemia was apparently caused by gastrointestinal bleeding and did not increase in severity after the operation. Myeloid hypoplasia of the type seen in his bone marrow has frequently been observed in cases of agranulocytosis caused by drug sensitivity or intoxication.

Of the other drugs the patient received, phenobarbital or nembutal might be thought capable of producing agranulocytosis. However, in 1934 the Council of Pharmacy and Chemistry of the American Medical Association, reviewed the published reports which suggested that barbiturates might cause agranulocytosis and concluded that "no definite case has been reported in which a barbiturate alone is responsible."<sup>16</sup> Hadler<sup>17</sup> and others have since reported patients in whom barbituric acid derivatives seemed to have caused granulocytopenia, but in none of these had phenobarbital or nembutal been responsible. It seems unlikely, therefore, that the barbiturate administration had an etiologic relationship to the agranulocytosis in the present case.

Although moderate degrees of leukopenia are frequently produced by therapy with sulfanilamide or its derivatives, agranulocytosis is a relatively rare complication. It rarely develops before the tenth to the fourteenth day after therapy is started.<sup>10</sup> Long and his associates<sup>7</sup> observed that it appeared most frequently between the seventeenth and twenty-fifth days, but might appear as late as the fortieth day of therapy. By this time, large amounts of the drug have usually been given. However, an occasional case has been reported in which relatively small total doses of the sulfonamides have produced agranulocytosis.<sup>11, 13</sup> The interval between initiation of therapy and the development of leukocytic depression has always been 14 days or more even though the duration of therapy and the total amount of drug administered have varied widely. This fact has suggested to a number of observers<sup>14, 15, 21</sup> that the time interval of 14 or more days is the time required for the development of a sensitivity to

the offending sulfonamide drug. It has been suggested that an individual who receives one of the sulfonamide substances a second time might develop agranulocytosis within a few days because of sensitivity produced during previous administration, but this occurrence has not as yet been reported. According to this concept, agranulocytosis produced by sulfonamide drugs is caused by a sensitivity to the chemotherapeutic agent analogous to amidopyrine sensitivity. It is interesting to note that the topical application of sulfathiazole has been observed to induce sensitivity characterized by fever and dermatitis.<sup>18, 20</sup> As far as could be ascertained, this patient had never received sulfanilamide prior to the implantation of five grams in his peritoneal cavity. It is difficult to believe that a dose so small could exert a direct toxic effect on the bone marrow sufficient to cause myeloid hypoplasia and agranulocytosis. The time interval of 17 days is sufficient to have allowed a sensitivity to develop. As far as the authors are aware, this is the first recorded instance in which agranulocytosis has been observed to follow the local or topical application of one of the sulfonamide drugs.

### SUMMARY

Description is given of a patient who developed acute agranulocytosis 17 days after five grams of crystalline sulfanilamide had been placed in his peritoneal cavity. Death occurred two days later. He had received no additional sulfanilamide and had not been exposed to other known leukotoxins.

### BIBLIOGRAPHY

1. Editorial: Intraperitoneal administration of sulfanilamide, *Jr. Am. Med. Assoc.*, 1942, cxix, 796-797.
2. MUELLER, R. S., and THOMPSON, J. E.: The local use of sulfanilamide in the treatment of peritoneal infections, *Jr. Am. Med. Assoc.*, 1942, cxviii, 189-193.
3. JACKSON, H. C., and COLLIER, F. A.: The use of sulfanilamide in the peritoneum, *Jr. Am. Med. Assoc.*, 1942, cxviii, 194-199.
4. WATSON, C. J., and SPINK, W. W.: Effect of sulfanilamide and sulfapyridine on hemoglobin metabolism, *Arch. Int. Med.*, 1940, lxxv, 825-846.
5. SAMS, W. M., and CAPLAN, L.: Topical treatment with sulfathiazole, *Arch. Dermat. and Syph.*, 1941, xlv, 226-230.
6. MILLER, J. L.: Use of sulfanilamide and its derivatives in ointment form: local treatment of cutaneous diseases, *Arch. Dermat. and Syph.*, 1942, xlv, 379-385.
7. LONG, P. H., and BLISS, E. A.: Clinical and experimental use of sulfanilamide, sulfapyridine and allied compounds, 1939, The MacMillan Co., New York.
8. LONG, P. H., HAVILAND, J. W., EDWARDS, L. B., and BLISS, E. A.: The toxic manifestations of sulfanilamide and its derivatives, *Jr. Am. Med. Assoc.*, 1940, cxv, 364-368.
9. SPINK, W. W.: Sulfanilamide and related compounds in general practice, 1941, The Year Book Publishers, Chicago, Ill.
10. KEEFER, C. S.: Sulfonamide: its mode of action and its use in treatment of various infections, *New England Jr. Med.*, 1938, ccxix, 562-571.
11. SPAIN, A. W.: Agranulocytosis following chemotherapy with small dosage, *Brit. Med. Jr.*, 1940, i, 930.
12. RINKOFF, S. S., and SPRING, M.: Toxic depression of the myeloid elements following therapy with the sulfonamides: report of 8 cases, *ANN. INT. MED.*, 1941, xv, 89-107.
13. GOLDMAN, L. M., APPLEBAUM, I., and ANTROPOL, W.: Malignant neutropenia following the use of sulfapyridine, *Am. Jr. Clin. Path.*, 1941, xi, 810-817.

14. SHECKET, N. A., and PRICE, A. E.: Fatal granulocytopenia following administration of sulfanilamide, *Jr. Am. Med. Assoc.*, 1939, cxii, 823-828.
15. PEARSON, H. E. S.: Fatal agranulocytosis after sulfanilamide therapy, *Brit. Med. Jr.*, 1939, i, 1031-1032.
16. Report of Council on Pharmacy and Chemistry: Relation of amidopyrine and barbituric acid derivatives to granulocytopenia, *Jr. Am. Med. Assoc.*, 1934, cii, 2183-2184.
17. HADLER, A. J.: Granulocytopenia following barbiturate therapy, *New England Jr. Med.*, 1940, ccxxii, 255-259.
18. LIVINGOOD, C. S., and PILLSBURY, O. M.: Sulfathiazole in eczematous pyoderma: sensitivity reaction to successive local and oral therapy, *Jr. Am. Med. Assoc.*, 1943, cxxi, 406-408.
19. COHEN, M. H., THOMAS, H. B., and KALISCH, M. D.: Hypersensitivity produced by the topical application of sulfathiazole, *Jr. Am. Med. Assoc.*, 1943, cxxi, 408-411.
20. WEINER, A. L.: Cutaneous hypersensitivity to topical application of sulfathiazole, *Jr. Am. Med. Assoc.*, 1943, cxxi, 411-413.

---

### HYPERPARATHYROIDISM, WITH FAILURE TO RECALCIFY AFTER REMOVAL OF PARATHYROID ADENOMA (A CASE REPORT) \*

By CHARLES P. VOLTZ, M.D., and KATHARINE SMULL, M.D.,  
*New York. N. Y.*

HYPERPARATHYROIDISM due to adenoma is usually followed by recalcification after removal of the tumor. The present report cites a case which was unusual in its failure to deposit calcium in the bones during a five year period after removal of the tumor, despite lack of evidence of a recurrence of hyperparathyroidism. The preoperative and immediate postoperative course of this patient was reported by Gutman and Parsons,<sup>1</sup> and it will only briefly be outlined here.

#### CASE REPORT

The patient, M. B., was a 54 year old Syrian spinster who was admitted to the Presbyterian Hospital in June 1937 with a 13 year history of repeated pathological fractures, with non-union, and subsequent skeletal deformities. There was no history of renal colic, polydipsia or polyuria. Roentgenography one and one-half years before admission (January 10, 1936) showed generalized skeletal decalcification in addition to cystic and fibrotic changes.

Examination on admission (June 14, 1937) showed marked skeletal deformities. The legs were atrophied, shapeless and bizarrely contorted. The pelvis was tilted to left. A rounded dorsal kyphosis was present. The skull was enlarged; the chin rested on the sternum because of shortening of the neck. Pronounced prognathism was present. There were obvious bony deformities of both arms. The bones of the legs were extremely tender to pressure, and there was some tenderness over the ribs, spine and arms. A nodular mass was palpable in the left side of the neck.

Laboratory data revealed: (1) Hypercalcemia (12.6 to 13.7 mg. per cent), hypophosphatemia (1.8 to 2.1 mg. per cent), and a consistently normal serum phosphatase

\* Received for publication July 27, 1942.

From First Medical Division, Welfare Hospital, and Department of Medicine, Columbia University.

level (2.7 to 3.0 Bodansky units). (2) Skeletal roentgenograms showing generalized decalcification of an extreme degree, especially of the lower legs, in which there were numerous cysts and in addition, cysts in the deformed and decalcified pelvis and in the ribs, which like the other bones were the seat of numerous fractures. (3) Normal blood count. (4) Normal urine except for a rare red blood cell. (5) Phenolsulfonphthalein excretion (intramuscular) of 37 per cent in two hours. (6) Calcium balance studies on a low calcium intake showing that the excretion of calcium in the urine (which is usually high in this condition) was not excessive.

Exploration in July 1937 revealed a tumor 2.0 by 1.2 by 0.5 cm. inferior to the left pole of the thyroid gland. The remaining parathyroid tissue was identified and no other parathyroid tumor was found. Histologically the mass removed was found to be a parathyroid adenoma. It was composed of chief cells, some of which were transitional to the water-clear type, and many rose-red cells.

Twenty-four hours after the removal of the tumor the serum calcium had fallen to 10.4 mg. per cent. The value a week previously had been 12.8 mg. per cent. The

TABLE I  
Preoperative and Postoperative Serum Calcium, Phosphorus and Phosphatase Values

Date	Ca. mg. %	P. mg. %	Phosphatase (Bodansky units)
7- 6-36	13.7	1.8	2.9
6-17-37	12.6	2.1	3.0
7- 2-37	12.8	1.9	2.7
7- 9-37	Parathyroid Tumor Removed		
7-10-37		2.4	2.7
7-12-37		2.8	2.2
7-14-37		2.4	3.1
7-19-37		2.7	3.3
7-13-38	10.0	2.9	2.5
2-28-39	10.1	3.6	2.9
8-22-39	9.5	3.1	3.0
4- 6-40	11.0	2.7	1.5
3- 5-41	10.5	2.7	2.6
9- 5-41	10.1	2.9	4.0
10-12-41	10.9	3.9	3.6
5- 4-42	9.4	3.7	2.4

patient was given 15 grams of calcium lactate a day for the six weeks following operation. A month postoperatively, roentgenogram revealed an elongated shadow of increased density in the region of the orifice of the left ureter. No such shadow was noted in roentgenograms taken a month before operation. This same shadow was still present in a roentgenogram of the kidney-ureter-bladder tract taken in December 1939. There had been no history of renal colic; urinalysis still showed a rare red blood cell. Phenolsulfonphthalein excretion (intramuscular) was 32 per cent in two hours in December 1942 as compared with 37 per cent in two hours before operation.

In 1942 the patient's status was very similar to that found immediately after operation. There had been no change in serum phosphatase activity, the values ranging from 1.5 to 4 Bodansky units; serum calcium values varied from 9.0 to 11.0 mg. per cent; serum phosphorus values lay between 2.4 and 3.9 mg. per cent. In July, 1941 the patient fractured the right tibia. The fracture healed by fibrous union but with no evidence of recalcification. Comparison of roentgenograms taken in November, 1941 with those of January, 1936 show an unchanged cystic and decalcified appearance of the bones despite the maintenance of normal serum calcium values (figures 1 and 2).

There has been no evidence of recurrence of hyperparathyroidism as seen from (1) normal serum calcium and phosphorus values, (2) calcium balance studies in August, 1939 showing that there has been no excessive urinary calcium excretion on a low calcium intake, (3) bone biopsy in August, 1939 showing an absence of osteoclasts and osteoblasts and suggesting that a long-standing condition had reached an equilibrium, (4) roentgenographic studies of the bones in November, 1941 showing no further decalcification.

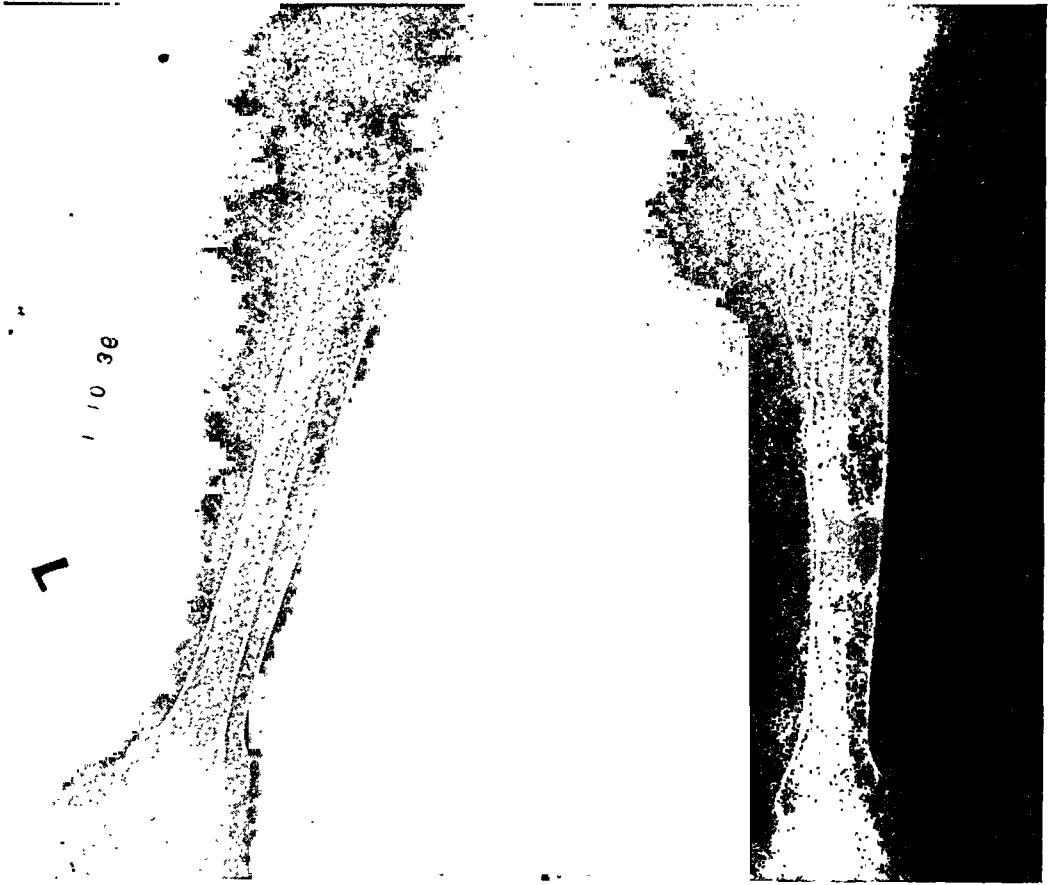


FIG. 1. (*Left*) Roentgenogram of the left leg taken one and one-half years before operative removal of parathyroid adenoma.

FIG. 2. (*Right*) Roentgenogram of same leg four years after removal of parathyroid adenoma showing no changes in the cystic and decalcified appearance of the bones.

#### DISCUSSION

Failure of recalcification in hyperparathyroidism due to adenoma after removal of the tumor might conceivably be related to two factors: the diminution of osteoblastic activity resulting in the lack of newly formed osteoid tissue; or, the absence of available calcium for deposit in the tissue.

This latter consideration seems unlikely because of adequate to excessive calcium intake, persistent normal serum calcium values and questionable renal calculus formation, the latter suggesting that adequate calcium was absorbed and available for deposition. Consequently, diminution in osteoblastic activity would



appear to offer the better explanation. A measure of this activity is reflected in the serum phosphatase level. In contrast to most cases of hyperparathyroidism with bone changes, the serum phosphatase level in this instance was not elevated previous to operation nor was it changed in the five subsequent years. As was suggested in the original paper by Gutman and Parsons, it is possible that when bone destruction is so extreme and of such long standing, osteoblastic activity comes to a standstill. The findings in this case lend weight to this hypothesis. It might, therefore be anticipated that in the absence of increased osteoblastic activity or of increased serum phosphatase levels, recalcification would not occur.

#### SUMMARY

(1) A case of hyperparathyroidism due to adenoma is presented. There was failure of recalcification five years following the removal of the tumor despite lack of evidence of recurrence of hyperparathyroidism.

(2) The failure of the bones to recalcify despite the prolonged normal serum calcium level is attributed to the lack of increased osteoblastic activity. Arrested osteoblastic activity is suggested by the normal preoperative and postoperative serum phosphatase levels.

#### BIBLIOGRAPHY

1. GUTMAN, A. B., and PARSONS, W. B.: Hyperparathyroidism simulating or associated with Paget's disease; with three illustrative cases, *ANN. INT. MED.*, 1938, xii, 13-31.

---

### UNCONTROLLABLE HEMORRHAGE AFTER DICOUMAROL THERAPY WITH AUTOPSY FINDINGS \*

By EDMUND L. SHLEVIN, M.D., and MAX LEDERER, M.D.,  
*Brooklyn, New York*

INTEREST in anti-coagulants as therapeutic agents has encouraged the trial of various substances in conditions characterized by intravascular clotting with resultant thrombosis and embolism. During the past few years heparin has occupied a leading rôle in this respect, until the discovery of the part played by spoiled sweet clover in the production of hemorrhagic disease of cattle.<sup>1</sup> The recognition of the active principal, dicoumarin (3,3' Methylenebis [4-Hydroxycoumarin]), its isolation and synthesis by Link and his coworkers,<sup>2</sup> have paved the way for its therapeutic employment in man.

Most reports thus far in the literature have described the beneficial results from its use, whereas others have also mentioned certain untoward effects attributed to it.<sup>3</sup> Its mode of action is as yet only slightly understood, its toxicity is but little known, and its usefulness, particularly as compared with heparin, questionable. In animals observed experimentally, toxicity is manifested by hemorrhages in muscles, aponeuroses, the gastrointestinal tract, pleural spaces and lungs. Marked dilatations of the capillaries, small arteries and veins have been noted, but no parenchymatous changes found.<sup>4</sup> In man, evidence of hemor-

\* Received for publication August 7, 1943.

From Departments of Medicine and Laboratories, Jewish Hospital of Brooklyn.

rhages in the urinary tract and intestines has been observed.<sup>11</sup> However, the following case with postmortem findings illustrates that severe hemorrhages contributing to death may attend the administration of dicoumarol.<sup>†</sup>

## CASE REPORT

K. O., female, 79 years of age, was admitted to the Jewish Hospital of Brooklyn on December 9, 1942, with hematuria of three days' duration and bleeding from the gums for five days. Four weeks before admission she complained of visual difficulty in her right eye. She was admitted to another hospital, where a diagnosis of "thrombosis of the right retinal vein" was made, following which, 100 mg. of dicoumarol were administered orally each day for 21 days. During this time no prothrombin estimations were made, although the coagulation time was found to be about 20 minutes. Four days before admission to the Jewish Hospital, bleeding from the gums was noted, and dicoumarol was discontinued. Two days later hematuria set in, which persisted up to the time of admission.

TABLE I

Date	C.T.	P.T.	C.	Remarks
Dec. 9	39'30"			Transfusion, oozing ceased
10	20'45"	60.6"	12.1"	Transfusion, oozing ceased
11	11'35"			
12	9'25"			Transfusion, oozing ceased
14	9'15"	96.8"	13.9"	
15				Oozing cardiac condition poor
16	49' +	360 + "	13"	Transfusion
17	20'	83.1"	11.2"	Ecchymoses, comatose, transfusion
18	11'20"	84.4"	12.8"	Transfusion
19				General ecchymoses, transfusion
21	28'30"			

C.T., Coagulation time (capillary tube method); P.T., Prothrombin time (Sherber method); C., Control.

Her past history disclosed a long standing hypertension and a "chronic anemia" for which 0.5 c.c. of reticulogen had been given every six weeks. She had had a gall-bladder operation many years before; no calculi were found and an appendectomy was performed.

*Physical Examination:* The patient was a coöperative and rational elderly female with normal temperature, pulse and respirations. The blood pressure was 200 mm. Hg systolic and 100 mm. diastolic. The pertinent physical findings were partial bilateral deafness, and regular, round, equal pupils which reacted to light and accommodation. Vision of the right eye was blurred. "In the region of the inferior temporal retinal vein on the right side, there was a large purplish hemorrhagic area extending out toward the macular region; there was moderate tortuosity of the vessels and slight arteriovenous inclining of both fundi; there was no exudate and the discs appeared normal." There was a slight bloody ooze from the gums. The heart was somewhat enlarged to the left, the sounds were distant and a soft systolic murmur was heard over the entire precordium. Over the extremities ecchymoses of different sizes were seen. The spleen and liver were not palpable. The clinical diagnosis was "generalized arteriosclerosis, hypertensive and arteriosclerotic cardiovascular disease, thrombosis of the right inferior temporal vein and bleeding secondary to dicoumarol ingestion."

The course in the hospital was a very eventful one. She was given a transfusion

<sup>†</sup> Dicoumarol is the trademark for the commercial preparation of Dicoumarin.

of 300 c.c. of fresh citrated blood on the day of admission. Following its administration, oozing from the gums ceased and the next morning there was no blood in the urine. However, on the following day, bleeding from the gums recurred, and she was given transfusions of 250 c.c. of citrated blood on the second and third days respectively. Bleeding ceased after these transfusions only to recur within the next 12 hours. During her stay she received a total of seven transfusions (table 1). Following the second, she developed acute left heart failure with marked cardiac irregularity due to premature auricular contractions. In the attempt to avoid myocardial embarrassment, subsequent transfusions were preceded by venesections. After the fourth hospital day she became dyspneic, orthopneic and cyanotic. Repeated phlebotomies were performed and she was given aminophyllin with transient relief. She then developed auricular fibrillation, digitalization was begun and she was placed in an oxygen tent. On the seventh day she had urinary retention for 24 hours. The following day progressive drowsiness set in, and she became unresponsive and incontinent. She grew progressively worse, lapsing into coma, and died on the fourteenth hospital day. The temperature ran an irregular course between 99° and 103° F., pulse rate between 70 and 100 per minute and the blood pressure gradually declined to 110 mm. of Hg systolic and 70 mm. diastolic.

#### AUTOPSY FINDINGS

*Gross:* The body was that of a well developed and well nourished elderly female 155 cm. in length and weighing 53 kg. There were varying sized ecchymotic areas on both shoulders, anus, hips and legs. The lips were pale. Most of the teeth were still present and were in fair condition. There was dried blood on the gums. The buccal mucosa was pale. In the retroperitoneal tissues of the left lower quadrant there was a large suffusion of blood.

The heart weighed 440 gm. The mitral valve cusps were slightly thickened. The aortic valve leaflets were thickened and there were calcified knobs on the free edges. There was no separation of the commissures. The ascending aorta was dilated to a circumference of 10.3 cm., at its widest portion. Within the wall of the entire aorta there were numerous, stony hard plaques. The coronary arteries were tortuous and their walls contained many calcified plaques which in places projected into the lumen. The trachea and bronchi contained a moderate amount of pink, frothy fluid. The lungs were buoyant and crepitant. On section the cut surfaces were pink-gray with areas of red especially in the lower lobes. Pink frothy fluid could be expressed from the surface on pressure.

The liver measured 29 by 12 by 7 cm. and weighed 1,100 gm. The external surface was brown, smooth and glistening. On section the color was deep mahogany. The markings were unusually distinct, pin head sized, deeper brown areas being separated from one another by slightly depressed grayish strands.

The spleen measured 12 by 8 by 2 cm. and weighed 90 gm. The capsule was slate blue in color. On section the fibrous markings were prominent.

The pancreas measured 17 by 6 by 4 cm. and weighed 80 gm. It was pink-gray in color, and the lobulations were distinct. The splenic artery was sclerotic and ran a tortuous course along the superior surface of the organ. Its wall contained many firm plaques.

The right kidney weighed 110 gm., the left 140 gm. The capsules stripped easily revealing a coarsely granular brown surface. On section, the markings were distinct. There were several irregularly shaped hemorrhagic areas in both pelves, more extensive in the left than in the right. Within the bladder wall there were many hemorrhages near the trigone. On section these appeared to be situated just beneath the mucosa (figure 1).

The marrow in the ribs and vertebrae was red-brown in color, and semi-fluid in consistency. In the right tibia the myeloid cavity was filled with bright yellow adipose tissue.

The cranial bones were unusually thick; the calvarium in the frontal region measured 1 cm. in thickness. The dura mater stripped from the bone fairly easily and was discolored red-brown. The vascular sinuses were not unusual, although the veins in the dura were prominent and dilated. In the subdural space, attached to the dura and covering the cerebral hemispheres was a layer of soft, jelly-like, red-blue, clotted blood, most of which could be reflected with the dura (figure 2). In the base



FIG. 1. Subdural hemorrhage, dura mater partially reflected.

of the skull, in the subdural space, especially in the middle fossae, similar extravasations were seen (figure 3). No lacerations of the meninges or fractures of the bones of the skull could be found; nor could any obvious source of the hemorrhage be demonstrated.

The brain weighed 1,220 gm. Loosely attached to the pia arachnoid over the right cerebrum was a membranous layer of gray fibrinous material. The pia arachnoid was delicate; the veins were widely dilated. There were collections of blood within the subarachnoid space. The gyri were narrower and the sulci broader than usual. The arteries at the base of the brain were elongated, tortuous, and their walls were almost stony hard in places. The left posterior cerebral artery was  $1\frac{1}{2}$  times as large

as the right. On section, the hemorrhage was seen to be restricted to the subarachnoid space, and no extravasations could be seen in the brain or ventricles.

*Microscopic: Heart and Aorta:* The blood vessels of the epicardium were greatly dilated and engorged. The myocardial cells were arranged in bundles separated by thin or moderately thick fibrous tissue trabeculae. The cells showed no unusual features, except in many places where delicate or coarse bundles of fibrous tissue lay between them. Here the myofibrils were swollen or shrunken, greatly distended, with granular pale staining cytoplasm and various sized nuclei. The coronary arteries showed a mild degree of sclerosis. The intima of the aorta was broad and wavy in



FIG. 2. Hemorrhage in base of skull.

outline, consisting chiefly of parallel lamellae of homogeneous pink staining material, separated in places by irregular plaques of lighter pink staining amorphous substance or clear boat-shaped clefts. Occasionally large collections of this pale staining material were seen, and in these the clefts were numerous. Masses of granular purple staining substance were also seen. In the media the muscle fibers and elastic fibers were separated in places by small variable sized irregular patches of violet staining amorphous material, and in others by elliptical shaped clefts. The adventitia was broad, being composed of adipose and fibrous tissue. A few small areas of perivascular round cell infiltration were seen.

*Lungs:* The alveoli varied much in size, most were larger than usual, and in some the septa were interrupted or missing. Many small patches of alveoli contained a pink staining, homogeneous, amorphous material, a few large mononuclear cells,

and some degenerated leukocytes. Occasionally there was an area in which the alveoli were slit-like and appeared to be compressed. In other places the parenchyma was replaced by large patches of fibrous tissue containing particles of black pigment and thickened blood vessels. The interalveolar septa throughout were prominent, the capillaries being greatly dilated and filled with blood. They thus presented a striking picture, especially in the edematous areas, where they stood out prominently in contrast to the pale staining coagulated edema fluid. The larger blood vessels, both arteries and veins, also were dilated and engorged. The bronchi in some places were collapsed, with narrow lumina, and stellate arrangement of the mucosa. In these the lumina were dilated and contained an amorphous granular material, leuko-



FIG. 3. Hemorrhage in pelves of kidneys and in urinary bladder.

cytes and much desquamated epithelium; the muscularis in these appeared thickened. In the submucosa there was a mild infiltration of polymorphonuclear neutrophilic leukocytes, small round and plasma cells. The medium sized and small arteries and veins, as well as the arterioles and venules were greatly dilated, and in most instances engorged with blood.

*Liver:* Glisson's capsule was composed of a broad layer of closely packed fibers which contained a few pale staining nuclei and assumed a wavy appearance. In the subcapsular regions there was a scattering of small and large round cells. The architectural pattern of the liver was distorted and disarranged. The lobules varied greatly in size, and were spherical, polygonal or irregular in shape. Many were surrounded by narrow or broad bands of fibrous tissue, composed of coarse or delicate strands, containing occasional oval, or spindle shaped, deeply staining vesicular nuclei.

In many there were focal or diffuse collections of small round cells and a few plasma cells. The normal relationship between portal areas, central veins and hepatic lobules was altered. In many of the lobules the liver cells were arranged in a crude cord-like fashion, many pseudo-cords anastomosing in a haphazard and irregular fashion. The usual radiating appearance was missing. The hepatic cells varied considerably in size; some were cuboidal, whereas others showed only a slight cuboidal or polyhedral shape. The nuclei varied a bit in size; all were spherical. The cytoplasm of most cells was coarsely granular; in others it contained vacuoles. In most of the latter the nuclei were situated at the periphery of the lobule in large groups, but a few smaller ones were seen in the central portion. With the Scharlach R stain on frozen sections, the contents of these vacuoles stained bright red. In a few scattered areas the cells were greatly swollen, the cell membranes were indistinct, the



FIG. 4. Hemorrhage in pia-arachnoid: dilatation of blood vessels.

cytoplasm was pale staining, finely granular and contained numerous small vacuoles. These areas were fairly well circumscribed. The Kupffer cells were fairly prominent. The sinuses were very wide and were filled with erythrocytes and a few leukocytes. In many of the portal areas there was a variable increase in fibrinous tissue and in some there were collections of small round cells. The portal veins and hepatic arteries were not increased in size or engorged.

*Kidneys:* The capsules were thickened, and made up of fibers containing a few small round cells. The number and distribution of glomeruli were as usual. A few showed transformation into hyaline amorphous structures, and some were surrounded by small amounts of fibrous tissue and focal infiltrations with small round cells. The tubular epithelium showed only some swelling and granular changes in places. In the pelvis between the muscularis and mucosa there was an extensive diffuse extravasation of blood. The wall of the urinary bladder was markedly thickened; beneath the mucosa was a large infiltration with blood.

*Spleen:* The capsule was composed of a broad layer of many connective tissue fibers, containing a few oval nuclei. The follicles appeared to be of the usual number, but were rather small, and in none were there germinal centers. The walls of the central arteries were thick; their lumina were narrow. The muscularis for the most part was replaced by broad bands of collagen or amorphous hyalinized material. They were surrounded by irregularly shaped islands of small round cells, the borders of which merged imperceptibly with the adjacent pulp. The latter appeared chiefly as a pattern of very loosely arranged spindle shaped cells, with long, delicate, anastomosing processes. Their nuclei were long, oval, vesicular and when vesicular, bulged into the lumen. The sinuses in most places were extremely large and dilated, containing many erythrocytes, some polymorphonuclear neutrophilic leukocytes, small and large round cells and a few immature myeloid elements. In some areas, there were large collections of blood, in which no splenic elements could be recognized.

*Lymph Node:* The capsule was thin; the follicles were ill-defined and in them the cells were scattered diffusely. They consisted chiefly of small and round cells and some polynuclear eosinophiles. The organ appeared to be the seat of a diffuse edema.

*Bone Marrow:* The vertebrae and ribs showed the usual distribution of hemopoietic and adipose tissue. From the tibia it consisted exclusively of adipose tissue.

*Meninges and Brain:* Sections taken from the cerebrum and cerebellum showed extensive extravasations of blood in the meshes of the pia-arachnoid, as well as in the subarachnoid and subdural spaces (figure 4). No coagulated material or fibrin could be recognized. The small arteries, veins and capillaries were greatly dilated and engorged with blood. Sections taken from various regions throughout the brain showed no unusual features.

*Pituitary Gland:* Showed a marked dilatation and engorgement of the capillaries.

*Anatomic Diagnosis:* Arteriosclerosis, generalized with particular involvement of: (a) coronary arteries with myofibrosis cordis; (b) aorta with aneurysmal dilatation; (c) renal arteries with nephrosclerosis; (d) cerebral arteries; hypertrophy and dilatation of heart; cirrhosis of liver; fibrous pleural and peritoneal adhesions; scars of operations; absence of appendix.

Hemorrhages in meninges, skin, retroperitoneal tissues, pelves of kidneys, urinary bladder, stomach and duodenum.

#### COMMENT

The main feature of the necropsy findings was the marked engorgement of all the blood vessels, excepting the larger trunks. It was most pronounced in the capillaries, arterioles and venules, and much more prominent than that usually seen post mortem in other conditions. The lumina of the vessels were broad and in all instances contained well preserved blood elements. In the liver and meninges, the impression was that of a relaxation of the vessel walls. Where the hemorrhages had occurred, no solution of continuity of the wall could be recognized. The probability is that such extravasations were due to diapedesis between cells, rather than to rupture or solution of continuity of the cell walls. This would explain the histologic picture and the rather limited foci of hemorrhage, especially where the bleedings were spontaneous and not connected with trauma however slight, as in the meninges and pelves of the kidneys. As a matter of fact, the hemorrhagic lesions resembled those seen in the purpuras, particularly the essential variety. The difference between the two, however, lies in the appearance of the blood vessels and sinuses. In the spleen it was striking in that the sinuses were greatly distended in many places, appearing as



pools of blood, bounded by intact sinus walls, with no obvious blood seepage. In the more extreme stage, frank hemorrhage with disappearance of splenic pattern was also seen. In the liver too, many places were seen with distended sinuses and clearly outlined cellular walls, filled with unchanged, unclotted blood. This is quite in accordance with the lesions produced in dogs by Bingham, Meyer and Pohle, after feeding dicoumarin in varying dosage.<sup>14</sup> No parenchymatous lesions were seen except occasionally some hydropic changes in the liver cells. In all dogs receiving fatal doses, hemorrhages were demonstrated at some site. All had some subcutaneous and intramuscular extravasations, while frequently evidence of hemorrhage was found in the gastrointestinal tract, pleural spaces or lungs. The dilatation of capillaries, small arteries and veins was especially striking in those animals dying acutely from massive doses. This was also observed sometimes to a lesser degree in animals receiving small doses and sacrificed for pathological study.

Whether the mild degree of cirrhosis of the liver contributed to the toxic action of dicoumarin in this case by exaggerating the prothrombin deficiency cannot be decided at this time. Certain observers<sup>11, 16</sup> suggest that dicoumarin interferes in some way with the prothrombin producing function in the liver and conclude that disease of the liver, or interference with its efficiency may be a predisposing factor to the establishment of a pathologic dicoumarin state and to the prolonged coagulation time of the blood. Assuming that this is likely, even though not proved, it cannot be the whole explanation for the hemorrhages. There still remains to be explained the extravasations that were found without any obvious lesions in the blood vessels. Here, the similarity to essential thrombocytopenia strikes one, with its multiple hemorrhages due apparently to some agent disturbing the normal permeability of the vascular system. Lalich, Lalich and Copley<sup>17</sup> suggest, as the result of experiments on mice receiving the hemorrhagic agent, that a deficiency of a hypothetical skin or tissue factor may play a rôle in the mechanism in producing the bleeding state.

The mechanism of blood coagulation is affected by dicoumarin through its action in producing a hypoprothrombinemia, as manifested experimentally and clinically<sup>12</sup> by a prolongation of prothrombin time. In this case, the prothrombin time was greatly increased, varying between 60.4 seconds to over 6 minutes.

The coagulation time was also significantly prolonged, but could be ameliorated temporarily by transfusion, as shown in table 1. This dicoumarin state with its abnormal clotting manifestation persisted for 18 days after the administration of dicoumarin had been discontinued, up to the time of death. Transfusions afforded a temporary means of restoring the normal clotting factors, probably through the instrument of the parenteral introduction of prothrombin. Clinically, this confirms the observations made by Prandoni and Wright,<sup>11</sup> Davidson and MacDonald,<sup>12</sup> and Barker, Allen and Waugh,<sup>16</sup> in regard to the behavior of the prothrombin and coagulation times in response to transfusion. The transitory benefit is sustained until the extraneous supply of prothrombin is exhausted. Bleeding then recurs and the previous dicoumarin state characterized by hypoprothrombinemia is resumed. There is no satisfactory explanation for this state, although clinical and experimental observations suggest that the dicoumarin interferes with prothrombin production at its source, rather than by acting as a neutralizing or inactivating agent of the prothrombin in the

blood stream or tissues. Whatever the mechanism, the prothrombin concentration is reduced to low levels during and persisting for some time after adequate dicoumarol administration.<sup>8</sup> Its continued use must be controlled uninterruptedly by prothrombin estimations. When the level falls to the danger point, the drug must be discontinued at once. If the latter is delayed until actual bleeding prevails, it may become impossible to control, as this case illustrates.

What is the dangerous level of prothrombin? Davidson and MacDonald<sup>12</sup> state that "the administration of dicoumarol should be controlled so that the prothrombin concentration be kept within reasonable limits." "However, to obtain a fairly constant and significantly delayed coagulability of the blood, one must reduce the prothrombin concentration to very low levels, and if this is done, the effect of the drug cannot be adequately controlled. Thus one must sacrifice control for effectiveness or vice versa." On the other hand, Bingham, Meyer and Howard<sup>13</sup> corroborating the experience of Butt, Allen and Bollman<sup>8</sup> and others, aim to maintain the prothrombin time not beyond 19 seconds (25 per cent) and the coagulation time between 15 and 20 minutes. Barker, Allen and Waugh<sup>14</sup> more recently in the study of 497 surgical cases advise sufficient dosage to secure a prothrombin time from 35 to 60 seconds, their normal being 18 to 22 seconds. We do not feel that this question can be answered with finality at present. Until this point is settled, it would appear that dicoumarol is a potent drug and its use still in the experimental stage.

#### CONCLUSIONS

1. A case is presented in which an uncontrollable dicoumarin state was produced.
2. Citrated transfusions were only partially and ineffectually successful in combating this state.
3. Uncontrollable bleeding due to dicoumarin action contributed to the death of this patient.
4. Dicoumarol should not be administered unless daily blood prothrombin and coagulation times can be accurately determined and the patient kept under close observation.

#### BIBLIOGRAPHY

1. SCHOFIELD, F. W.: Damaged sweet clover: The cause of a new disease in cattle simulating hemorrhagic septicemia and blackleg, *Jr. Am. Vet. Med. Assoc.*, 1924, lxiv, 553-575.
2. CAMPBELL, H. A., ROBERTS, W. L., SMITH, W. K., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease I, *Jr. Biol. Chem.*, 1940, cxxxvi, 47-55.
3. CAMPBELL, H. A., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease IV, *Jr. Biol. Chem.*, 1941, cxxxviii, 21-33.
4. CAMPBELL, H. A., SMITH, W. K., ROBERTS, W. L., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease II, *Jr. Biol. Chem.*, 1941, cxxxviii, 1-20.
5. HUEBNER, C. F., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease VI, *Jr. Biol. Chem.*, 1941, cxxxviii, 529-534.
6. OVERMAN, R. S., STAHPMAN, M. A., SULLIVAN, W. R., HUEBNER, C. F., CAMPBELL, H. A., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease VII, *Jr. Biol. Chem.*, 1942, cxlii, 941-954.
7. STAHPMAN, M. A., HUEBNER, C. F., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease V, *Jr. Biol. Chem.*, 1941, cxxxviii, 513-527.

8. BUTT, H. R., ALLEN, E. V., and BOLLMAN, J. L.: A preparation from spoiled clover which prolongs coagulation and prothrombin time of the blood—preliminary report of experimental and clinical studies, *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 388-395.
9. LEFEVRE, F. A.: The effect of 3,3' Methylene-Bis(4-Hydroxycoumarin) Dicoumarol on the prothrombin and coagulation time of the blood, *Cleveland Clin. Quart.*, 1942, ix, 147-152.
10. TOWNSEND, S. R., and MILLS, E. S.: The effect of the synthetic hemorrhagic agent 3,3' Methylene-bis(4-Hydroxycoumarin) in prolonging the coagulation and prothrombin time in the human subject, *Jr. Canad. Med. Assoc.*, 1942, xlv, 214-218.
11. PRANDONI, A., and WRIGHT, I. S.: The anti-coagulants heparin and the dicoumarin 3,3' Methylene-Bis(4-Hydroxycoumarin), *Bull. New York Acad. Med.*, 1942, xviii, 433-455.
12. DAVIDSON, C. S., and MACDONALD, H.: Critical study of action of 3,3' Methylenebis (4-Hydroxycoumarin) dicoumarin, *Am. Jr. Med. Sci.*, 1943, ccv, 24-33.
13. BINGHAM, J. B., MEYER, O. O., and HOWARD, B.: Studies on the hemorrhagic agent 3,3' Methylenebis (4-Hydroxycoumarin) III, *Am. Jr. Med. Sci.*, 1943, ccv, 587-594.
14. BINGHAM, J. B., MEYER, O. O., and POHLE, F. J.: Studies on the hemorrhagic agent 3,3' Methylenebis (4-Hydroxycoumarin) I, *Am. Jr. Med. Sci.*, 1941, ccii, 563-578.
15. MEYER, O. O., BINGHAM, J. B., and AXELROD, V. H.: Studies on the hemorrhagic agent 3,3' Methylenebis (4-Hydroxycoumarin) II, *Am. Jr. Med. Sci.*, 1942, cciv, 11-21.
16. BARKER, N. W., ALLEN, E. V., and WAUGH, J. M.: The use of dicoumarol (3,3' Methylenebis) 4-Hydroxycoumarin in the prevention of postoperative thrombophlebitis and pulmonary embolism, *Proc. Staff Meet. Mayo Clin.*, 1943, xviii, 102-107.
17. LALICH, J. J., LALICH, M. H., and COPLEY, A. L.: Bleeding time in mice following oral administration of 3,3' Methylene-bis (4-Hydroxycoumarin), *Surgery*, 1943, xiii, 316-321.

## EDITORIAL

### HISTOPLASMOSIS

INFECTION with the yeast-like organism histoplasma was first reported in 1906 by Darling, who discovered three cases of the infection in the course of a systematic search for kala azar in the Canal Zone. Clinically the disease in Darling's <sup>1</sup> cases was "characterized by splenomegaly, emaciation, irregular pyrexia, leukopenia and anemia." The pathologic lesions he described as "the invasion of endothelial cells in the smaller lymph and blood vessels and capillaries by enormous numbers of a small encapsulated organism (*Histoplasma capsulatum*) causing necrosis of the liver with cirrhosis, splenomegaly, pseudogranuloma of the lungs, small and large intestines with ulceration of the latter, and necrosis of the lymph nodes draining the infected viscera." He regarded the organism as a protozoan parasite.

The disease was long regarded as a rare tropical infection, since 20 years elapsed before another case was reported (by Watson and Riley in Minnesota in 1926). Since 1934, however, cases have been reported in increasing number, and over 60 cases have now been recorded in more or less detail. Most of these have been in the United States, in which the disease is widely distributed from California to Florida, to Maryland, to Minnesota, and in many intermediate states. Cases have also been reported in Java, the Philippines, Argentina, Brazil and Central America. The disease is evidently widely distributed, and probably is much commoner than has been realized.

In many of these cases diagnosis depended entirely upon morphological demonstration of the organisms in tissues at autopsy, but in a number of them (at least nine) the organism has been cultivated from the blood or tissues before or after death, and positively identified.

In the tissues the organisms are found chiefly within large mononuclear phagocytes (reticuloendothelial cells), although extracellular organisms have been observed. There may be only a few organisms within a cell, but often the cells are densely packed with them. The organism is round or oval in outline, usually 3 to 5 micra in diameter, occasionally larger. In stained preparations there is a small, deeply staining mass of chromatin which may appear as a spherical or crescentic body more or less centrally located, surrounded by a clear area and enclosed in a highly refractile capsule which does not take any of the ordinary stains. There is no accessory chromatin dot or kinetoplast such as is found in the Leishman-Donovan bodies of kala azar.

When grown in cultures, the organism appears in two forms. In cultures directly from the body grown on blood agar at 37° C., it appears as yeast-like cells which multiply by budding. In older cultures or those grown at room temperature the yeast-like cells grow out into slender, branching,

<sup>1</sup> DARLING, S. T.: The morphology of the parasite (*Histoplasma capsulatum*) and the lesions of histoplasmosis, a fatal disease of tropical America, Jr. Exper. Med., 1909, xi, 515.

septate mycelia and form white, fluffy, cotton-like colonies with aerial hyphae which bear large spores 8 to 13 micra in diameter at the tips of the branches or stalked along the hyphae. It has been difficult to make the mycelial form revert to the yeast-like form in cultures, but when susceptible animals are infected with cultures in the mycelial stage, the organisms appear in their tissues in the yeast-like form.

The organism was first cultivated by DeMonbreun<sup>2</sup> from the blood of an infant with a disseminated infection, in whom the diagnosis had been made before death by Dodd and Tompkins<sup>3</sup> by demonstrating the organism in the monocytes in blood films. DeMonbreun was the first to establish the nature of the parasite as a fungus. He produced infection in monkeys, dogs and mice by inoculation of cultures. Redaelli and Ciferri<sup>4</sup> reported successful infection of rabbits and guinea pigs, and Reid et al.<sup>5</sup> infected guinea pigs by intraperitoneal injections. Parsons<sup>6</sup> also infected mice by intravenous injection, producing a disseminated infection similar to that in man.

The lesions in experimental infections in the main closely resemble those in human cases. In the earlier stages of an acute disseminated infection, phagocytes stuffed with parasites may occur in masses or sheets in the organs with little or no evidence of inflammatory reaction. In somewhat later stages, typically small tubercle-like lesions are produced, with a necrotic caseous central area surrounded by granulomatous tissue in which there are many phagocytes containing parasites. In late stages the lesions become fibrosed, and it may be difficult or impossible to find parasites. Such lesions may occur in any organ containing reticuloendothelial cells, particularly in the spleen, liver and deep lymph nodes, and often in the lung. Extensive necroses of the adrenal glands have occurred in a number of cases. There may be ulcerative lesions of the skin, the buccal or laryngeal mucous membrane or of the colon.

Although organisms are found mainly in reticuloendothelial phagocytes, they have also been found in the cells of the adrenal cortex and medulla, the epithelial cells of the liver as well as the Kupffer cells, in glandular epithelium of the larynx, in acinar epithelium of the prostate and rarely in neutrophilic leukocytes.<sup>7</sup>

An excellent review of the clinical and pathological features of the earlier

<sup>2</sup> DEMONBREUN, W. A.: Cultivation and cultural characteristics of Darling's *Histoplasma capsulatum*, Am. Jr. Trop. Med., 1934, xiv, 93-125.

<sup>3</sup> DODD, KATHERINE, and TOMPKINS, EDNA: A case of histoplasmosis of Darling in an infant, Am. Jr. Trop. Med., 1934, xiv, 127-137.

<sup>4</sup> REDAELLI, P., and CIFERRI, R.: Etudes sur "l'*histoplasma capsulatum*" Darling; reproduction expérimentale de l'histoplasmose (etc.), Soc. internaz. de microbiol., Boll. d. sez. ital., 1934, vi, 193-195.

<sup>5</sup> REID, J. D., et al.: Systemic histoplasmosis; systemic histoplasmosis diagnosed before death and produced experimentally in guinea pigs, Jr. Lab. and Clin. Med., 1942, xxiv, 419-434.

<sup>6</sup> PARSONS, R. J.: Experimental histoplasmosis in mice, Arch. Path., 1943, xxiv, 229-239.

<sup>7</sup> VAN PERNIS, P. A., BENSON, M. E., and HOLINGER, P. H.: Laryngeal and systemic histoplasmosis (Darling), ANN. INT. MED., 1943, xviii, 384-393.

cases was published by Meleney<sup>8</sup> in 1940, and more recently Boltjes<sup>9</sup> has reviewed the subject on the basis of 30 collected cases in which reasonably adequate clinical as well as pathological data were available. The clinical manifestations of the disease vary markedly depending upon the extent and distribution of the lesions and the acuteness of the infection. The disease occurs as a generalized infection running a rapidly progressive course with a fatal outcome within a few weeks or months, particularly in young individuals. In less acute cases, lesions may be predominantly localized in one or a few tissues or organs. Isolated areas of histoplasma infection, particularly in the lungs or adrenal glands, have been described as incidental findings in individuals dying of some other unrelated disease.

The generalized type of infection is characterized by protracted irregular fever, weakness, emaciation, progressive anemia and usually a leukopenia with reduction in the granular leukocytes. The liver and spleen are almost always enlarged, often markedly so, and this is clinically evident in about 80 per cent of the cases. Lymph nodes are enlarged in about two-thirds of the cases, but the deep nodes such as the peribronchial or mesenteric are primarily affected, and notable enlargement of the superficial nodes occurs only occasionally. The parasites have been demonstrated in the monocytes of the circulating blood in several of these cases, and in them the organism has been obtained in blood cultures.<sup>2, 5, 10</sup> In at least five cases organisms have been demonstrated in sternal marrow smears, but negative results have been obtained in some cases. This type of the disease resembles kala azar.

Pulmonary lesions, sometimes with pleural involvement, have been described in about half the cases. In several, such as two reported by Meleney<sup>11</sup> these dominated the clinical picture. These cases resemble chronic tuberculosis, and in several cases there was an associated tuberculosis.

In about one-third of the cases intestinal ulcers have occurred, with parasitized phagocytes in the walls or base of the ulcers. Less frequently there may be a severe chronic diarrhea, suggesting a chronic ulcerative colitis, as in the case of Henderson et al.<sup>12</sup>

In another group the presenting lesions have been chronic granulating ulcers in the buccal or pharyngeal mucous membrane or in the larynx. Van Pernis et al.<sup>7</sup> have reported such a case, associated with extensive lesions in the adrenals and many of the clinical manifestations of Addison's disease. Ulcerative lesions of the skin have also been reported.

<sup>8</sup> MELENEY, H. E.: Histoplasmosis (reticuloendothelial cytomycosis): a review, *Am. Jr. Trop. Med.*, 1940, xx, 603-616.

<sup>9</sup> BOLTJES, B.: Histoplasmosis. Report of a case with brief review of the literature, *Jr. Kansas Med. Soc.*, 1943, xlv, 226-229.

<sup>10</sup> WRIGHT, R. B., and HACHTEL, F. W.: Histoplasmosis of Darling; report of a case, *ANN. INT. MED.*, 1941, xv, 309-319.

<sup>11</sup> MELENEY, H. E.: Pulmonary histoplasmosis; report of two cases, *Am. Rev. Tuberc.*, 1941, xlv, 240-274.

<sup>12</sup> HENDERSON, R. G., PINKERTON, H., and MOORE, L. T.: *Histoplasma capsulatum* as a cause of chronic ulcerative enteritis, *Jr. Am. Med. Assoc.*, 1942, cxviii, 885-889.

Broders et al.<sup>13</sup> have reported one case in which there was a mycotic vegetative endocarditis in a heart previously damaged by rheumatic fever. The diagnosis had been established by biopsy of the liver, but the endocarditis was not recognized until autopsy, when large numbers of parasites were found in the vegetations.

The prognosis in histoplasmosis appears to be unfavorable, since with one exception every case recognized during life has died. Meleney<sup>8</sup> mentioned one patient who was treated with neostam, a pentavalent antimony preparation, because he was thought erroneously to have kala azar, and who made at least a temporary clinical recovery. Thus far, however, only severe progressive cases have been recognized. Unless the disease were suspected and a biopsy carried out, there is at present no means of making a diagnosis in mild cases, if they occur. In the chronic cases there appears to be a definite tendency for the tubercle-like lesions to heal with disappearance of the parasites. It seems probable that some cases recover or become arrested.

The mode of infection is not known, although the skin, the respiratory and gastrointestinal tracts have been suggested as portals of entry. De-Monbreun found a dog naturally infected, and he was able to infect dogs by feeding cultures of histoplasma. Morphologically similar organisms have been found in ferrets and in mice. It is possible, therefore, that man might be infected by such animals. The organism has not been found naturally outside the body.

It is evident from this brief review that histoplasmosis may simulate many types of subacute and chronic infections. It should be considered as a possibility in infections of obscure nature, particularly of the types mentioned. Diagnosis can be established with certainty only by cultivation of the organism, although its morphological appearance is so distinctive as to make possible a diagnosis with a high degree of probability. This may be best accomplished by biopsy of a suspicious lesion if one is accessible. Examination of stained films of the blood and sternal marrow and cultures of the blood should reveal the organisms in many cases of disseminated infection. If these are unsuccessful, puncture or biopsy of the liver or spleen may be carried out. Using as antigen a filtrate of a broth culture, Van Pernis et al.<sup>7</sup> obtained positive intracutaneous reactions in one patient, and in experimentally infected mice, whereas negative reactions were obtained in controls. Further study is required to determine the value of this procedure.

<sup>13</sup> BRODERS, A. C., et al.: Histoplasmosis producing vegetative endocarditis; review of the literature and report of a case, *Jr. Am. Med. Assoc.*, 1943, cxxii, 489-491.

## REVIEWS

*A Textbook of Pathology.* Fifth Edition. Edited by E. T. BELL, M.D., Professor of Pathology, University of Minnesota. 862 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1944. Price, \$9.50.

The fifth edition of Bell's "Textbook of Pathology" maintains the high standards established in previous editions. This edition includes new material on shock, the vitamin deficiencies, blast injuries, Boeck's sarcoid and certain infectious diseases of military interest. The early chapters deal with toxics of a fundamental pathological nature, whereas later chapters are devoted to the special pathology of the various organs and systems. The textual material is concise, the exposition clear and the bibliographies at the end of each section are brief, but well chosen. Illustrations are uniformly good. The typography and format of the book are excellent. This volume can be heartily recommended to any student of pathology, be he undergraduate or graduate. As a ready reference work in pathology, it should merit a prominent place in the library of the practicing physician.

M. S. S.

*Handbook of Nutrition.* A Symposium Prepared under the Auspices of the Council on Foods and Nutrition of the American Medical Association. (Reprinted from the Journal of the American Medical Association with Additions.) 579 pages; 14.5 × 22 cm. American Medical Association, Chicago. 1943. Price, \$2.50.

The *Handbook of Nutrition* is a comprehensive and concise review of all phases of nutrition and the chemistry and physiology connected with it. It includes much material intended primarily for physicians but also of interest to dietitians. The latest developments in research on vitamins and other dietary factors are here. Each chapter in the book is written by a different author, each outstanding in the fields of nutrition, medicine, or commercial research. Every one is well qualified to write on his subject. It contains a great deal of practical and interesting information and should be very useful as a reference book to both physicians and nutritionists. Abundant reference material is listed in the footnotes all the way through the book. A few of the authors are E. V. McCollum, Professor of Biochemistry at Johns Hopkins University; James S. McLester, Chairman of the Council on Foods and Nutrition of the American Medical Association; H. C. Sherman, Professor of Chemistry, Columbia University; Hazel K. Stiebelling, Assistant Chief, Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture; Edward F. Kohman, Research Chemist, Campbell Soup Company.

The first eleven chapters are concerned with the specific dietary factors, their functions, the latest results of research on them, the requirement for optimum health, and other pertinent information. The essential amino acids and their nature are discussed at length in the chapter on proteins. It is suggested that certain amino acids may be eliminated from the diet in some pathological conditions but as yet, not enough is known about the subject to make it practical. The best sources of amino acids are still the good animal and vegetable protein foods. The chapter called *Calories in Medical Practice* takes up the calculation of caloric requirement, the way calories should be distributed among the various food groups in the diet, and the use of this energy in the body.

The chapters on vitamins are particularly interesting because there is so much new material on them. The two chapters are *The Fat Soluble Vitamins* and *The Water Soluble Vitamins*. The aim in the discussion of vitamins in this book is to present the latest material. The reader is referred to a symposium on vitamins printed



by the American Medical Association in 1939 for the older basic and fundamental facts about vitamins. A few of the interesting facts given may be mentioned. In general the fat soluble vitamins are stored in much larger quantity than the water soluble ones. Ninety-five per cent of the vitamin A is stored in the liver, and this amount increases with age. A good amount is supplied for the very tiny baby as early human milk has from five to ten times the biologic activity of vitamin A of cow's milk. Since the water soluble vitamins are so little stored, it is very necessary to get the requirement daily. Vitamin K is the vitamin concerned with the amount of prothrombin in the blood and consequently the clotting power. In general, a deficiency of K is observed only in new-born infants. This has been explained as follows. Vitamin K is supplied to the body mainly by bacteria in the intestinal tract rather than in the food. The deficiency in the new-born child occurs because these bacteria have not yet had a chance to develop. Administration of K corrects the condition.

The chapter on Preservation of the Nutritive Value of Foods in Processing is important because of the great amount of food preservation being done now. Improving the Quality of Cheap Staple Foods is interesting as it tells what the government is doing to try to improve the diet of the average person and those with a low income. A table giving the current standards of enrichment and fortification of some foods is given. The foods to which these standards pertain are white flour enriched with thiamin, riboflavin, niacin and iron; oleomargarine with vitamin A; milk with vitamin D; and table salt with iodides. The chapter called Feeding the Aged is enlightening and throws light on a subject which often seems to be neglected. With the elimination and control of many diseases which occur early in life, there are coming to be more and more "older people." In order that they shall not be a liability their vitality must be preserved with the aim "to add life to years rather than years to life," and this is largely a matter of nutrition. Doctors must guide older people in their dietary habits and the essence of this guidance is not in restricting their diets, but in keeping it well balanced with plenty of protein and calories, and a little less fat. The last three chapters are of practical interest mainly to physicians. They are concerned with organic maladies affecting the use of food in the body and physical examinations of patients for malnutrition.

Besides being practical and useful, this book is broadening to the education of both doctors and dietitians.

M. F.

### BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*The Analysis and Interpretation of Symptoms.* Edited by CYRIL M. MACBRYDE, M.D. (Reprinted from Clinics, April, 1944; Vol. II, No. 6—pages 1343-1644.) 301 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Co., Philadelphia. Price, \$4.00.

*Physical Medicine in General Practice.* By WILLIAM BIERMAN, M.D. 654 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, \$7.50.

*The Diabetic Life. Its Control by Diet and Insulin.* 13th Edition, with war-time supplement. By R. D. LAWRENCE, M.A., M.D., F.R.C.P. (London). 228 pages; 21 × 14 cm. 1944. The Blakiston Company, Philadelphia. Price, \$4.00.

*Psychiatry and the War.* (A Record of the Conference on Psychiatry held at Ann Arbor, Michigan, October 22, 23, and 24, 1942, at the Invitation of the University

- of Michigan and McGregor Fund.) Edited by FRANK J. SLADEN, M.D. 505 pages; 23.5 × 16 cm. 1944. Charles C. Thomas, Springfield, Illinois. Price, \$5.00.
- The International Bulletin for Medical Research and Public Hygiene.* Vol. A44—Poliomyelitis—By EDWARD C. ROSENOW, M.D. (Editor-in-Chief: W. L. COLZE.) 87 pages; 23 × 15.5 cm. 1944. From the Mayo Foundation for Medical Education and Research, University of Minnesota, Rochester. Printed by Drechsel Printing Company, New York City.
- International Organization for Health.* By C.-E. A. WINSLOW, M.D. 32 pages; 21 × 14 cm. 1944. Commission to Study the Organization of Peace, New York City. Price, \$.10 (25 or more copies—10% discount).
- Bacterial Infection with Special Reference to Dental Practice.* 3rd Edition. By J. L. T. APPLETON, B.S., D.D.S., Sc.D. 498 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia. Price, \$7.00.
- The Electrocardiogram. Its Interpretation and Clinical Application.* By LOUIS H. SIGLER, M.D., F.A.C.P. 403 pages; 23.5 × 16 cm. 1944. Grune & Stratton, Inc., New York City. Price, \$7.50.
- Secretory Mechanism of the Digestive Glands.* By B. P. BABKIN, M.D., D.Sc., LL.D., F.R.S.C. 900 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York City. Price, \$12.75.
- Principles and Practices of Inhalational Therapy.* By ALVAN L. BARACH, M.D. 315 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Co., Philadelphia. Price, \$4.00.
- Artificial Pneumothorax in Pulmonary Tuberculosis.* By T. N. RAFFERTY, M.D. Introduction by HENRY STUART WILLIS, M.A., M.D. 192 pages; 22.5 × 15 cm. 1944. Grune & Stratton, Inc., New York City. Price, \$4.00.
- Infections of the Peritoneum.* By BERNHARD STEINBERG, M.D. With a foreword by FREDERICK A. COLLIER, M.S., M.D. 455 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York City. Price, \$8.00.
- Pensamentos.* By RENATO KEHL (da Academia de Medicina, Rio de Janeiro e Lima). 29 pages; 16.5 × 12 cm. 1942. Livraria Francisco Alves, Paulo de Azevedo & Cia, Rio de Janeiro.
- Hipertension Arterial Nefrogena.* By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCILO, LUIS F. LELOIR, JUAN M. MUÑOZ, and ALBERTO C. TAQUINI. 475 pages; 23 × 16 cm. 1943. El Ateneo, Buenos Aires.
- Cancer Primitivo del Pulmon. Estudio Clinico Quirurgico.* By ERNESTO ESCUDERO. 542 pages; 23 × 16 cm. 1943. Libreria Hachette S. A., Buenos Aires.
- Medical Education in the United States before the Civil War.* By WILLIAM FREDERICK NORWOOD, Associate Professor of the History of Medicine and Associate Dean in the School of Medicine, College of Medical Evangelists, Los Angeles. Foreword by HENRY E. SIGERIST. 487 pages; 24 × 16 cm. 1944. University of Pennsylvania Press, Philadelphia. Price, \$6.00.

## COLLEGE NEWS NOTES

### ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Previously reported in the News Notes section of this journal were the names of 1,071 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,706.

William L. Cover  
Albert C. Santy

Laurance W. Kinsell  
Frederick Steigmann

Morgan Y. Swirsky

Major Robert E. Lyons, Jr., (MC), AUS—honorably discharged October 8, 1943.

---

### NEW LIFE MEMBER

Dr. Harold H. Jones, F.A.C.P., Winfield, Kan., became a Life Member of the College on June 24, 1944.

---

### GIFTS TO THE COLLEGE LIBRARY

The following gifts are gratefully acknowledged:

#### *Books*

- Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—“The Electrocardiogram, Its Interpretation and Clinical Application.”  
Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio—“Collected Papers from the Department of Physiology, Western Reserve University School of Medicine—Volume X, Studies on Shock.”

#### *Reprints*

- J. Edward Berk, F.A.C.P., Captain, (MC), AUS—1 reprint.  
Charles A. Bohnengel, F.A.C.P., Captain, (MC), AUS—1 reprint.  
Dr. Alexander G. Davidson, F.A.C.P., Brooklyn, N. Y.—2 reprints.  
Arden Freer, F.A.C.P., Colonel, (MC), USA—1 reprint.  
Dr. I. W. Held, F.A.C.P., New York, N. Y.—1 reprint.  
Irving R. Juster, F.A.C.P., Major, (MC), AUS—1 reprint.  
Morgan Y. Swirsky, (Associate), Lieutenant, (MC), AUS—3 reprints.  
Leon H. Warren (Associate), Lieutenant Colonel, (MC), AUS—1 reprint.  
Dr. Mast Wolfson, F.A.C.P., Monterey, Calif.—1 reprint.  
Dr. Edwin E. Ziegler, F.A.C.P., Bethlehem, Pa.—1 reprint.

---

Communication from the Royal College of Physicians, Pall Mall East, S. W. 1, London:

“22nd May, 1944

Dear Sir:

I think it would be a very good idea if you would announce in the *ANNALS OF INTERNAL MEDICINE* the fact that Fellows of the American College of Physicians will be welcome to lectures at this College. We advertise these lectures in the *Lancet*, *British Medical Journal* and the *British Times* newspaper, so that anyone interested can inform himself of the title and date. I think, therefore, that these arrangements will cover it for the immediate future.

I was very interested to meet Colonel (William S.) Middleton the other day, when we were delighted to admit him a Fellow of this College. I first met him in France during the last War. We spoke together of this subject, and he said that he would like to help in making members of your College now in this Country, au fait with our invitation.

Yours truly,

(Signed) H. E. A. BOLDERO  
*Registrar*

To The Executive Secretary, The American College of Physicians"

---

#### HARVARD MEDICAL SCHOOL ENCOURAGES STUDY OF LEGAL MEDICINE

Dr. Frank R. Ober, Assistant Dean of Harvard Medical School, recently announced that the graduate department with the coöperation of the Medical Schools of Boston University and Tufts College has planned a condensed one-day conference and a more extensive seminar in legal medicine. No attempt will be made to turn out medico-legal specialists, but the object is to give to the average medical examiner, coroner, or other physician interested in the subject, a clearer, general working knowledge, in order that he can better perform his day-to-day duties.

The Massachusetts Medico-Legal Society, in conjunction with the aforementioned institutions, has arranged for an all-day Conference, to be held at the Mallory Institute of Pathology, Boston City Hospital, Wednesday, October 4, 1944. It will include lectures, demonstrations and informal discussions concerning many subjects in legal medicine, particularly stressing some of the more recent procedures. There will be no registration fee, and the meeting will be open to any registered physician, lawyer, police official, senior medical student, or other medical investigator who may be interested. Advance application is not essential, but it will be helpful to those arranging the Conference if notice of intention to attend is sent prior to October 1 to Dr. W. H. Watters, Department of Legal Medicine, Harvard Medical School, Boston.

The Seminar in legal medicine will be given at Harvard Medical School, Courses for Graduates, during the entire week of October 2-7. It is planned particularly for medical examiners and coroners' physicians, but will be open to any suitable graduate of an approved medical school. The course will be practical rather than theoretical, and will consist of autopsy demonstrations, technique and interpretation of laboratory tests, study of the day-by-day cases of a medical examiner, round-table conferences and many other subjects included within the widening field of legal medicine. The Seminar fee is \$25.00, and enrollment will be limited to fifteen applications, which should be filed before October 1, with Harvard Medical School, Courses for Graduates, 25 Shattuck Street, Boston 15, Mass.

---

#### PHYSICIAN-ARTISTS' PRIZE CONTEST

The American Physicians Art Association, with the coöperation of Mead Johnson & Company, is offering an important series of War Bonds as prizes to physicians in the Armed Services and also physicians in civilian practice for their best artistic works depicting the medical profession's "skill and courage and devotion beyond the call of duty."

Announcement of further details will be made soon by the Association's Secretary, Dr. F. H. Redewill, Flood Building, San Francisco, Calif.

In the June, 1944, number of the ANNALS OF INTERNAL MEDICINE, page 1009, was published the names of the members of the College from the United States who attended the inaugural meeting of the new National Institute of Cardiology at Mexico City, as guests of the Mexican Government. From this list was inadvertently omitted the name of Dr. Joseph Kopecky, F.A.C.P., of San Antonio, Texas. We regret the omission.

---

The New York Institute of Clinical Oral Pathology announces its first open meeting to be held at the New York Academy of Medicine, October 30, 1944, in Hosack Hall. The symposium will be devoted to "Fluorine and Dental Caries." Members of the medical, dental and public health and other professional groups are cordially invited. Further information is available through the Executive Secretary, 101 E. 79th Street, New York 21, N. Y.

---

Dr. Roger I. Lee, F.A.C.P., former President of the American College of Physicians, of Boston, has been elected President-Elect of the American Medical Association, and will be inducted to the Presidency at the New York meeting of that society next year.

---

Dr. A. C. Ivy, F.A.C.P., Dr. J. A. Roth and Dr. A. J. Atkinson, of Northwestern University Medical School, Chicago, were awarded the bronze medal in Group I of the scientific exhibits of the American Medical Association at Chicago during June. Their exhibit dealt with the effect of caffeine on the formation of ulcers.

---

Dr. George Dock, F.A.C.P., Los Angeles, Calif., was the recipient of the Distinguished Service Medal of the House of Delegates of the American Medical Association for 1944. Dr. Dock is noted for his work on the pathology of malaria and dysentery, protozoan diseases of the blood, pernicious anemia, the ductless glands and hookworm.

From nominations submitted to the Committee on Distinguished Service Award, five names are selected and passed on to the Board of Trustees, which in turn selects three for submission to the House of Delegates. The three names presented for 1944 were those of Dr. Isaac A. Abt, of Chicago, Dr. George Dock, of Los Angeles and Dr. Simon Flexner, of New York.

---

#### MINNEAPOLIS PUBLIC LIBRARY STAGES A MEDICAL ART SHOW

The Minneapolis Public Library, from June 21 to July 22, staged an unique art show, representing the work of leading medical artists the country over. It is part of a program for extending the services of the Public Library to one of the important medical centers in the United States. A display of rare medical books and prints formed an important part of the exhibit. The Surgeon General's Office in Washington supplied four books showing the earliest examples of anatomical drawings. A copy of the 1783 Vesalius from the library of Dr. Shirley Miller of the University of Minnesota, and photostatic copies of early anatomies were on display.

---

Captain William Stein, (MC), AUS, (Associate), formerly of New Brunswick, N. J., has been made the Chief of the Medical Services of the 313th Station Hospital overseas.

Dr. Burrell O. Raulston, F.A.C.P., Los Angeles, Calif., has been appointed by the Section on the Practice of Medicine of the American Medical Association a member of the American Board of Internal Medicine, effective July 1, 1944, succeeding Dr. Ernest E. Irons, F.A.C.P., Chicago, who has served as Chairman of the Board for some years.

Dr. Reginald Fitz, F.A.C.P., Boston, has been appointed Chairman. Other additions to the Board include Dr. Frederic M. Hanes, F.A.C.P., Durham, N. C., and Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Minn., both appointees of the American College of Physicians.

---

Colonel Howard A. Rusk, (MC), U. S. Army, F.A.C.P., formerly of St. Louis, recently received an award of \$1,000.00 for outstanding contributions to the rehabilitation of the war injured. The presentation was made at the Lord and Taylor Seventh Annual American Design Awards luncheon at the Waldorf-Astoria, New York City, on April 20. Colonel Rusk is now Chief of the Convalescent Branch, Office of the Air Surgeon, Washington, D. C.

---

Dr. J. Q. Griffith, F.A.C.P., Philadelphia (with Wilfred Fry) received a certificate of merit for an exhibit on "choked disk" at the meeting of the American Medical Association in Chicago during June.

---

Dr. Julius H. Comroe, Sr., F.A.C.P., York, Pa., recently received the Civilian Service Award in recognition of his faithful service as Chief of the Cardiac Specialists at the Harrisburg Armed Forces Induction Center. Dr. Comroe, during the past two years and seven months devoted over 690 days to the examination of selectees.

---

Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., has been elected an Honorary Member of the Sociedad Chilena de Tisologia.

---

Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., was inducted as President of the American College of Chest Physicians at its tenth annual meeting in Chicago, June 10-12, 1944. Major General Shelley U. Marietta, F.A.C.P., Washington, D. C., was elected Second Vice President.

---

Dr. B. P. Seward, F.A.C.P., Roanoke, Va., has been elected a Vice President of the Roanoke Academy of Medicine.

---

Dr. Anthony Bassler, F.A.C.P., New York City, showed a moving picture on "Treatment of Intestinal Amebiasis" before the recent meeting of the National Gastroenterological Association in New York, June 7. Dr. Linn J. Boyd, F.A.C.P., New York City, gave a paper on "Liver Function Tests: A Study of 600 Cases." Dr. Hyman I. Goldstein (Associate), Camden, N. J., discussed "Post-War Malaria," a paper presented before the meeting by Dr. Isidore Snapper.

---

The twenty-second annual fall clinical conference of the Kansas City Southwest Clinical Society will be held at Kansas City, October 2-3-4, 1944. Among the guest speakers will be Dr. Russell L. Haden, F.A.C.P., Cleveland, and Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor.

Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, delivered a paper before the Section on Gastro-enterology and Proctology of the American Medical Association at Chicago, June 14, on "Gastro-duodenal Dyssynergia."

---

Dr. Benjamin W. Black, F.A.C.P., Oakland, Calif., was chairman at ceremonies at which Cutter Laboratories, Berkeley, Calif., were awarded the Army-Navy E pennant for outstanding achievement in war production. Dr. Black asserted that Cutter Laboratories' production of blood plasma, vaccines and penicillin is unequalled in the world.

---

Dr. Francis G. Blake, F.A.C.P., Regent of the College and Dean of Yale University School of Medicine, will be the chairman of the twentieth clinical congress of postgraduate medicine of the Connecticut State Medical Society, New Haven, September 28-29.

---

Dr. Gerardo M. Balboni, F.A.C.P., Boston, was recently appointed a member of the Massachusetts State Board of Registration in Medicine.

---

Dr. Benjamin A. Shepard, F.A.C.P., Kalamazoo, recently retired because of ill health as Medical Director of the Pine Crest Sanatorium, Oshtemo, Mich. The Sanatorium has been taken over by the State Sanatorium Commission and will be known as the Pine Crest State Sanatorium.

---

Dr. Edgar E. Evans (Associate), Penns Grove, N. J., addressed the New Jersey Association of Industrial Physicians at Newark, June 30, on "Hydrofluoric Acid Burns and Their Treatment."

---

#### DR. STRECKER RECEIVES STRITTMATTER AWARD

Dr. Edward A. Strecker, F.A.C.P., Professor of Psychiatry and Chairman of the Department, University of Pennsylvania School of Medicine, recently was awarded the Strittmatter Award of the Philadelphia County Medical Society "in recognition of his distinguished service in the field of psychiatry and mental hygiene and his unselfish devotion to the highest ideals of the profession as physician, teacher, author and consultant in civilian and military medicine."

---

#### COLONEL PINCOFFS RECEIVES LEGION OF MERIT AWARD

Colonel Maurice C. Pincoffs, F.A.C.P., Regent of the College and Editor of the ANNALS OF INTERNAL MEDICINE, formerly Professor of Medicine at the University of Maryland School of Medicine and now Chief of Professional Services of the Southwest Pacific area, was recently awarded the Legion of Merit for experimental work in malaria control. Colonel Pincoffs has been on active service since April 20, 1942.

---

#### CIVILIAN CONSULTANTS NAMED AS ADVISERS TO THE ARMY MEDICAL DEPARTMENT

Nineteen civilian specialists have been recently appointed as a board of advisers to the Office of the Surgeon General. Among these appointees are Dr. Walter L.

Palmer, F.A.C.P., Chicago, and Dr. Chester M. Jones, F.A.C.P., Boston, (gastro-enterology); Dr. Paul D. White, F.A.C.P., Boston, and Dr. Robert L. Levy, F.A.C.P., New York, (heart disease); Dr. Chester S. Keefer, F.A.C.P., Boston, (chemotherapy); Dr. Francis M. Rackemann, F.A.C.P., Boston, and Dr. Robert A. Cooke, F.A.C.P., New York, (allergy); Dr. James J. Waring, F.A.C.P., Denver, and Dr. J. Burns Amberson, Jr., F.A.C.P., New York, (tuberculosis).

---

Dr. Hugh B. Campbell, F.A.C.P., Norwich, is Treasurer of the Connecticut State Medical Society. Dr. Campbell recently resigned as Superintendent of the Norwich State Tuberculosis Sanatorium, Uncas-on-Thames, to become Medical Director of the Phoenix Life Insurance Company of Hartford. He has been succeeded by Dr. William H. Weidman, F.A.C.P., who heretofore has been Senior Sanatorium Physician.

---

Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., has retired from the faculty of Georgetown University School of Medicine as special lecturer in medical economics, but retains his position as Professor of Clinical Radiology. The Executive Secretary of the Medical Society of the District of Columbia, Mr. Theodore Wiprud, has been appointed Professor of Medical Socio-economics, succeeding Dr. Christie.

---

At its fourth annual meeting, Chicago, June 11, the American Diabetes Association initiated and made awards of the Banting Memorial Medal to all ex-presidents and to all lecturers of the Association. The medal memorializes Sir Frederick Banting, F.A.C.P., discoverer of insulin, who at the time of his death was the honorary president of the American Diabetes Association. Among those receiving the medals were Dr. Cecil Striker, F.A.C.P., Cincinnati; Dr. Herman O. Mosenthal, F.A.C.P., New York; Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia; Dr. Elliott P. Joslin, F.A.C.P., Boston; and Col. Leonard G. Rowntree, (MC), AUS, F.A.C.P.

Two medals will be awarded annually in the future—one to the outgoing president and one to the lecturer.

Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, was elected the new president and Drs. Russell M. Wilder, F.A.C.P., Rochester, Minn., and Edward S. Dillon, F.A.C.P., Philadelphia, were elected vice presidents. Dr. Cecil Striker was reelected secretary.

---

At the annual meeting of the American Gastro-enterological Association at Chicago, June 13, Dr. A. H. Aaron, F.A.C.P., Buffalo, was elected president; Drs. Henry L. Bockus, F.A.C.P., Philadelphia, and Walter L. Palmer, F.A.C.P., Chicago, vice presidents; Dr. John G. Mateer, F.A.C.P., Detroit, treasurer; and Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., secretary. The next annual meeting will be held in Atlantic City, May, 1945.

---

Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, was recently elected president-elect of the American Society of Clinical Pathologists. Dr. J. J. Moore, F.A.C.P., Chicago, was reelected vice president.

---

Dr. Ellen C. Potter, F.A.C.P., Director of Medicine, New Jersey State Department of Institutions and Agencies, Trenton, was made president of the National Conference on Social Work, May 27.



Dr. William H. Perkins, F.A.C.P., Dean and Professor of Preventive Medicine, Jefferson Medical College, Philadelphia, addressed the New Castle County Medical Society and the Delaware Academy of Medicine at Wilmington, Del., May 16, on "Tropical Diseases of Concern to the Home Front."

---

Dr. William Cabell Moore, F.A.C.P., Washington, D. C., has retired as Medical Director of the Chesapeake and Potomac Telephone Company, a position he has held since March, 1922, and will be succeeded by Dr. R. Lomax Wells, F.A.C.P., Washington, D. C.

---

Dr. Robinson Bosworth, F.A.C.P., East St. Louis, Ill., received the Dearholt Medal of the Mississippi Valley Conference on Tuberculosis, May 10. Dr. Bosworth is Medical Director of Pleasant View Sanatorium. The citation accompanying the medal referred to his contribution to the development of sanatoriums for the treatment of tuberculosis and declared him "a pioneer in the development of standards for outpatient work."

---

On May 22, members of the Chicago Society of Internal Medicine elected Dr. Lee C. Gatewood, F.A.C.P., as president and Dr. George E. Wakerlin, F.A.C.P., vice president.

---

The Medical Society of the State of North Carolina, at its recent annual meeting, installed Dr. Paul F. Whitaker, F.A.C.P., Kinston, as president and elected Dr. William H. Smith, F.A.C.P., Goldsboro, a vice president.

---

Dr. Sidney A. Slater, F.A.C.P., Worthington, Minn., has served six years as president of the Minnesota Public Health Association. Recently the Association presented him with a gold wrist watch as a token of appreciation and recognition.

---

Dr. Howard K. Petry, F.A.C.P., Harrisburg, has been appointed Chairman of a board to survey Pennsylvania State institutions for the care of the mentally ill.

---

#### STATE OF WASHINGTON CONSIDERS NEW MEDICAL SCHOOL

The Washington State Medical Association has appointed a Committee of which Dr. George H. Anderson, F.A.C.P., Spokane, and Dr. David C. Hall, F.A.C.P., Seattle, are members to study the feasibility of establishing a medical school in connection with the University of Washington at Seattle.

---

#### TWO FELLOWS PROMOTED TO RANK OF BRIGADIER GENERAL, U. S. ARMY

Colonel George B. Foster, Jr., F.A.C.P., and Colonel Henry C. Dooling, F.A.C.P., were recently advanced to the rank of Brigadier General in the Medical Corps of the United States Army. Both are members of the "regular" corps.

---

Dr. Reginald Fitz, F.A.C.P., Boston, Regent of the College, was elected president elect of the Massachusetts Medical Society during its last annual meeting, May 22-24.

The New York Diabetes Association is conducting for the ninth consecutive season, a camp (Camp Nyda) for diabetic boys and girls at Walkill, N. Y. Dr. Frederick W. Williams, F.A.C.P., is in charge of the medical department.

---

Dr. Mary Riggs Noble, F.A.C.P., Bowmansdale, Pa., is treasurer of the American Medical Women's Association.

---

New officers of the American Therapeutic Society elected at its Chicago meeting, June 10, include Dr. Edward Sterling Nichol, F.A.C.P., Miami, Fla., president; Drs. Thomas J. Coogan, F.A.C.P., Chicago, Ill., and Charles L. Hartsock, F.A.C.P., Cleveland, Ohio, vice presidents; Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C., secretary.

---

Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, Va., has been elected to the Council of the American Psychiatric Association.

---

Dr. Robert H. Riley, F.A.C.P., Baltimore, Md., has been made Chairman of the Maryland Postmortem Examiners Commission. Dr. Riley is Director of the State Department of Health.

---

The Alumni Association of the Medical College of the State of South Carolina has established a lectureship to honor Dr. Robert Wilson, Sr., F.A.C.P., recently retired Dean.

---

On the fifth morning of the American College of Physicians' graduate course given last April at the Massachusetts General Hospital. Dr. Alpheus F. Jennings of Detroit asked for the floor. The doctors, said he, had found the course interesting and particularly they liked the approach, namely, that of resting clinical practice squarely on a sound scientific foundation. As a material token of their satisfaction the doctors asked the Hospital to accept a purse which they had made, and devote it to some purpose of research. It contained three hundred and ten dollars.

This purse was accepted. To this sum has been added the balance of the tuition fees, after expenses had been paid, making a total of one thousand one hundred and two dollars and fifty-nine cents. This has been turned over to the Treasurer of the Massachusetts General Hospital to be held as a special fund—the "ACP Fund." It will be used toward the salary of, or travel for, some young investigator or investigators of promise, probably after demobilization has begun.

Those participating in conducting the course and the American College of Physicians as a whole are very grateful to the doctors taking the course for their gracious action.

---

Dr. Arthur P. Richardson, Head of the Department of Pharmacology of the University of Tennessee, has been appointed Head of the Division of Pharmacology of the Squibb Institute for Medical Research, to become effective on October 1, 1944. Dr. Richardson will replace Dr. H. B. VanDyke, who has accepted the position as Head of the Department of Pharmacology, College of Physicians and Surgeons, Columbia University.

Dr. Richardson is a native of Longmont, Colorado, but obtained his A.B. and M.D. degrees at Stanford University (California) in '32 and '37 respectively. While taking his doctoral degree, he was assistant in pharmacological research ('33-'36),

and then remained at Stanford as instructor in Pharmacology ('37-'38); and later as assistant professor ('39-'41). He spent a year as National Research Council Fellow at Johns Hopkins ('38-'39). He then became visiting associate professor at the University of Tennessee Medical School, Memphis, Tennessee ('41), where he has since remained as associate professor ('41-'43), professor ('43-) and head of the department ('41-).

Dr. Richardson's chief interests have been in the field of chemotherapeutic research, and he has had very extensive experience in studies concerning malaria and other tropical diseases. For the past two years he has been primarily engaged in the study of antimalarial compounds.

#### EXAMINATIONS BY CERTIFYING BOARDS

AMERICAN BOARD OF INTERNAL MEDICINE, William A. Werrell, M.D., Assistant Secretary-Treasurer, 1301 University Avenue, Madison 5, Wisconsin.

*Written Examinations:* October 16, 1944, in various centers throughout the United States; also available to candidates in military and naval services at certain of their stations, with permission of their medical commanding officers. All applications for civilian candidates should be filed by August 15, 1944. Every effort will be made to accommodate candidates in the Service, regardless of the closing date for the acceptance of applications.

*Oral Examinations:* Consult Assistant Secretary-Treasurer; oral examinations will probably be given just preceding the annual meeting of the American College of Physicians in the early spring of 1945, and also just preceding the annual meeting of the American Medical Association in the late spring of 1945. If the Board finds it possible to conduct regional examinations during 1944, an announcement will appear in the ANNALS OF INTERNAL MEDICINE and the Journal of the American Medical Association.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY, C. Guy Lane, M.D., Secretary, 416 Marlboro Street, Boston, Massachusetts.

Consult the Secretary concerning examination schedule for autumn of 1944 and spring of 1945.

AMERICAN BOARD OF PEDIATRICS, C. A. Aldrich, M.D., Secretary, 115½ First Avenue, S. W., Rochester, Minnesota.

*Written Examination:* September 22, 1944, locally under monitors.

*Oral Examinations:* St. Louis, Missouri, November 8-9, 1944, and New York City, December 15-16, 1944. Closing date for filing applications, August 15, 1944.

AMERICAN BOARD OF PATHOLOGY, F. W. Hartman, M.D., Secretary-Treasurer, Henry Ford Hospital, Detroit, Michigan.

Consult the Secretary-Treasurer for future schedule.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, Walter Freeman, M.D., Secretary, 1028 Connecticut Avenue, N. W., Washington, D. C.

Consult the Secretary for future schedule. At last advice, this Board will schedule an examination in New York City about the middle of December, 1944. However, the dates for both the written and oral examinations will not be set until late autumn or early winter.

AMERICAN BOARD OF RADIOLOGY, B. R. Kirklin, M.D., Secretary, Mayo Clinic, Rochester, Minnesota.

This Board conducts only a general oral examination. Next examination, Chicago, Illinois, September 22-23-24, 1944.

---

#### A. C. P. POSTGRADUATE COURSES

Consult the inside back cover for complete schedule of courses to be offered during the autumn of 1944:

The detailed Bulletin, descriptive of all courses, will be printed during August and distributed about September 1. However, reservations may be entered through the Executive Offices of the College at any time.

The full details of the course in Cardiology, being complete when this issue goes to press, are hereunder published.

#### COURSE No. 1—CARDIOLOGY

(October 2-7, 1944)

MASSACHUSETTS GENERAL HOSPITAL

Boston, Mass.

PAUL D. WHITE, M.D., F.A.C.P., *Director*

(Minimal Registration 30; Maximal Registration 50)

#### OFFICERS OF INSTRUCTION

Donald G. Anderson, M.D., Research Fellow in Medicine, Evans Memorial and Massachusetts Memorial Hospitals; Instructor in Medicine, Boston University School of Medicine.

Joseph C. Aub, M.D., Physician, Massachusetts General Hospital; Director of Medical Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University at the Massachusetts General Hospital; Professor of Research Medicine, Harvard Medical School.

William B. Breed, M.D., F.A.C.P., Physician, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Associate in Medicine, Harvard Medical School.

C. Sidney Burwell, M.D., F.A.C.P., Research Professor of Clinical Medicine and Dean, Harvard Medical School.

Benjamin Castleman, M.D., Acting Director of Department of Pathology and Bacteriology, Massachusetts General Hospital; Instructor in Pathology, Harvard Medical School.

Mandel Cohen, M.D., Assistant Psychiatrist, Massachusetts General Hospital; Instructor in Psychiatry, Harvard Medical School.

Lewis Dexter, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Instructor in Medicine, Harvard Medical School.

Robert E. Gross, M.D., F.A.C.S., Associate Visiting Surgeon, Children's Hospital; Associate in Surgery, Peter Bent Brigham Hospital; Assistant Professor of Surgery, Harvard Medical School.

Burton E. Hamilton, M.D., F.A.C.P., Cardiologist, Boston Lying-In Hospital and New England Deaconess Hospital; Clinical Associate, Thorndike Memorial Laboratory, Boston City Hospital.

T. Duckett Jones, M.D., Director of Research, House of the Good Samaritan; Assistant Physician, Massachusetts General Hospital; Assistant Professor of Medicine, Harvard Medical School.

Otto Kraye, M.D., Associate Professor of Comparative Pharmacology and Head of Department, Harvard Medical School.

Eugene M. Landis, M.D., F.A.C.P., Higginson Professor of Physiology, Harvard Medical School.

Samuel A. Levine, M.D., F.A.C.P., Physician, Peter Bent Brigham Hospital; Assistant Professor of Medicine, Harvard Medical School.

Robert R. Linton, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

Benedict Massell, M.D., Assistant in Medicine, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Assistant in Medicine, Harvard Medical School.

Sylvester McGinn, M.D., Lieutenant Commander, (MC), USNR, Assistant in Medicine, Massachusetts General Hospital; Assistant in Medicine, Harvard Medical School.

James H. Means, M.D., F.A.C.P., Chief of the Medical Services, Massachusetts General Hospital; Jackson Professor of Clinical Medicine, Harvard Medical School.

Joseph E. F. Riseman, M.D., Associate Visiting Physician, Beth Israel Hospital; Associate in Medicine, Harvard Medical School.

Reginald H. Smithwick, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

Merrill C. Sosman, M.D., Roentgenologist-in-Chief, Peter Bent Brigham Hospital; Clinical Professor of Roentgenology, Harvard Medical School.

Howard B. Sprague, M.D., F.A.C.P., Captain, (MC), USNR, Associate Physician, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Instructor in Medicine, Courses for Graduates, Harvard Medical School.

Richard H. Sweet, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

James C. White, M.D., F.A.C.S., Captain, (MC), USNR, Chief of Neurosurgical Service, Massachusetts General Hospital; Assistant Professor of Surgery, Harvard Medical School.

Paul D. White, M.D., F.A.C.P., Physician, In Charge of Cardiac Clinics and Laboratory, Massachusetts General Hospital; Lecturer in Medicine, Harvard Medical School.

Conger Williams, M.D., Assistant in Medicine, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Assistant in Medicine, Courses for Graduates, Harvard Medical School.

This course in the diagnosis and treatment of cardiovascular disease has been arranged to give in one week a summary of the recent advances and present status of our knowledge of cardiovascular disease with particular emphasis on clinical aspects. Some attention is directed also to the fundamental principles of cardiovascular anatomy, physiology, pharmacology and pathology. Authorities in their respective fields who are available to take part have been enlisted, including a number of physicians who have made important contributions to our knowledge of cardiovascular disease. Illustrative cases will be presented. The course will be limited to fifty.

#### OUTLINE OF COURSE

Monday, October 2.

A.M. Session

9:00-10:00 Anatomy of the Heart and Great Vessels.

Dr. White.

10:00-11:00 Practical Considerations in Cardiovascular Physiology.

Dr. Landis.

11:00-12:00 Cardiovascular Pharmacology.

Dr. Krayner.

12:00- 1:00 Electrocardiography.

Dr. White.

P.M. Session

2:00- 3:00 Precordial Leads in Electrocardiography.

Dr. Williams.

3:00- 4:00 Cardiovascular Roentgenology.

Dr. Sosman.

4:00- 5:00 Case Problems in Cardiovascular Roentgenology.

Dr. White.

Tuesday, October 3.

A.M. Session

9:00-10:00 Cardiovascular Symptoms.

Dr. White.

10:00-11:00 Cardiac Auscultation.

Dr. Levine.

11:00-12:00 Blood Pressure, Normal and Abnormal.

Dr. Dexter.

12:00- 1:00 Peripheral Circulation—Anatomy and Physiology.

Dr. Linton.

P.M. Session

2:00- 3:30 Cardiovascular Pathology.

Dr. Castleman.

3:30- 5:00 Case Problems in Cardiovascular Pathology.  
Dr. White.

Wednesday, October 4.

A.M. Session

9:00-11:00 Congenital Heart Disease with Cases.  
Dr. White.

11:00- 1:00 Rheumatic Fever and Rheumatic Heart Disease, with Cases.  
Dr. Jones and Dr. Massell.

P.M. Session

2:00- 3:00 Cardiovascular Syphilis.  
Dr. Hamilton.

3:00- 4:00 Hypertensive Heart Disease.  
Dr. White.

4:00- 5:00 The Cor Pulmonale, Acute and Chronic.  
Dr. McGinn.

Thursday, October 5.

A.M. Session

9:00-11:00 Coronary Heart Disease.  
Dr. Sprague.

11:00-12:00 Medical Grand Rounds. Cardiac Cases.  
Dr. Means and Dr. Breed.

12:00- 1:00 Clinicopathological Conference. Cardiovascular Cases.

P.M. Session

2:00- 3:00 Subacute Bacterial Endocarditis.  
Dr. Anderson.

3:00- 4:00 Pericarditis, Acute and Chronic.  
Dr. Burwell.

4:00- 5:00 Diseases of Arteries and Veins.  
Dr. Linton.

Friday, October 6.

A.M. Session

9:00-10:00 Congestive Heart Failure. Diagnosis.  
Dr. White.

10:00-11:00 Congestive Heart Failure. Treatment.  
Dr. Williams.

11:00-12:00 Arrhythmias. Diagnosis.  
Dr. Levine.

12:00- 1:00 Arrhythmias. Treatment.  
Dr. Williams.

P.M. Session

2:00- 3:00 Shock.  
Dr. Aub.

3:00- 4:00 Neurocirculatory Asthenia.  
Dr. Cohen.

4:00- 5:00 Special Notes on Cardiovascular Drugs.  
Dr. Riseman.

5:00- 6:00 Motion Picture, "Angina Pectoris."  
Dr. Riseman.

Saturday, October 7.

A.M. Session

9:00-12:00 Cardiovascular Surgery.

Dr. White, Dr. Smithwick, Dr. Gross and Dr. Sweet.

12:00- 1:00 Concluding Exercise. The Future of Cardiovascular Disease.  
Dr. White.

#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

#### *Rhoads General Hospital, Utica, New York*

August 17 Wounds of the Extremities and Their Management. Dr. Roscoe Severance

Note: Program has been arranged by Capt. J. Edward Berk of this installation.

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman;  
Dr. N. C. Gilbert, Dr. W. H. Cole.

#### *Mayo General Hospital, Galesburg, Illinois*

Sept. 6 Arthritis { Rheumatoid—Acute Rheumatic Fever  
Osteo-arthritis  
a. Other bone diseases

#### *Camp Ellis, Illinois*

Sept. 6 Laboratory Diagnosis—and its relationship to treatment  
a. Hypoproteinemia—Alkalosis—Acidosis—Dehydration—  
Electrolytic balance

#### *Camp McCoy, Wisconsin*

Sept. 6 Orthopedic Problems of General Interest  
a. Low back pain—Foot and Knee Strain—March Fracture, etc.

#### *Camp Grant, Illinois*

Sept. 6 Symposium on Organic Neurology  
a. Central and Peripheral

#### *Truax Field, Wisconsin*

Sept. 6 Psychiatry—Psychoneurosis—Neurocirculatory Asthenia—Malingerer,  
etc.

#### *Chanute Field, Rantoul, Illinois*

Sept. 6 Peptic Ulcer and Gastritis  
a. Diagnosis and medical care  
b. Surgical approach



## CORRECTION IN ANNOUNCEMENT RE ROYAL COLLEGE OF PHYSICIANS

In the May, 1944, issue of this journal announcement was made of the invitation from the Registrar of the Royal College of Physicians, Pall Mall East, S.W. 1, London, to members of the American College of Physicians to attend the advanced Lectures of the Royal College, given each month from November to July. The announcement should have referred specifically to *Fellows* of the American College of Physicians, because facilities at the Royal College are inadequate at the present time to accommodate also Associates of the American College of Physicians.

Fellows of the American College of Physicians desiring to have their names placed on the mailing list for such invitations may communicate their desires to Dr. G. A. Pemberton Wright, Royal London Ophthalmic Hospital, (Moorfields Eye Hospital), City Road, E. C. 1, London, who will be glad to certify such Fellows to the Registrar of the Royal College of Physicians. It is, of course, important that Fellows, when writing to Dr. Wright, include their mailing addresses.

## OBITUARIES

## COLONEL PATRICK S. MADIGAN

Colonel Patrick S. Madigan, 57, an officer of the Regular Army Medical Corps for 27 years, died May 8, 1944, at Fort Belvoir, Va., where he was on duty as commanding officer of the station hospital. Burial was in Arlington National Cemetery.

Colonel Madigan was born in Washington, D. C., Feb. 18, 1887. He was graduated from Georgetown University College of Liberal Arts in 1908 and from the medical college of the University in 1912, serving as a member of the Georgetown faculty from 1913 to 1917. He held the degree of Master of Arts and the honorary degree of Doctor of Laws and Letters from Gonzaga College.

Colonel Madigan began his Army medical career as a first lieutenant in the Medical Corps of the Regular Army in 1917 and served in France with the 7th Division, 6th Infantry.

Following the Armistice he returned to this country and for several months was stationed at Hampton Roads, Va. From 1920 until 1926 he was chief of the neuropsychiatry section at the Walter Reed General Hospital in Washington, and during that period studied at the Army Medical School in Washington and at the Medical Field Service School, Carlisle Barracks, Pennsylvania. Following his tour of duty in Washington, Colonel Madigan was ordered to the Philippine Islands where he was chief of the neuropsychiatry section at Sternberg General Hospital in Manila for two years. He returned to Walter Reed in 1928, and later was sent to the Canal Zone where he was on duty for four years, returning to the United States in 1936. He was then assigned to the station hospital at Fort Sam Houston, Texas, as assistant executive officer and chief of the neuropsychiatry section.

Colonel Madigan was appointed medical advisor to the Surgeon General in Washington in 1940 and held that post for eight months before assignment as commanding officer of the station hospital at Camp Lee, Va. He remained there until his transfer to Fort Belvoir in February of this year.

Colonel Madigan was a Fellow of the American College of Physicians and of the American Medical Association.

He leaves his wife, Mrs. Mary Shugree Madigan; two sons, Emmet P. Madigan, a first lieutenant in the Army Medical Corps and Gerald P. Madigan, a student at Georgetown Preparatory School; two brothers, Colonel John J. Madigan, also of the Army Medical Corps, Dr. Joseph P. Madigan; and three sisters, Misses Margaret and Mary Madigan and Mrs. A. Levin, all of Washington.

MAJOR GENERAL NORMAN T. KIRK, (MC), USA,  
A.C.P. Governor for the U. S. Army

## DR. CLARENCE JAMES MCMULLEN

Dr. Clarence James McMullen, Fellow of the American College of Physicians since 1940, died May 25, 1944, at the age of 54.

Dr. McMullen was born at Des Moines, Iowa, in 1890, and received his early education in Chicago, Ill. He graduated from Illinois College of Medicine in 1912, and took a postgraduate course in cardiology under Dr. Paul D. White at the Massachusetts General Hospital. From 1914 to 1926 he served as Instructor and subsequently as Associate Professor of Medicine at the University of Illinois College of Medicine. The ensuing two years were spent at Rush Medical College, Chicago, where he was Assistant Professor of Medicine. For 15 years, between 1923 and 1938, Dr. McMullen was Attending Physician at Cook County Hospital, Chicago, where he also became Consulting Physician on diabetes.

In addition to being a Fellow of the American College of Physicians, he was a member of the Chicago Medical Society, Chicago Society of Internal Medicine, and the American Medical Association.

Failing health cut short a promising career at the age of 48, and Dr. McMullen died a few years following his retirement to Los Angeles, California.

ROY E. THOMAS, M.D., F.A.C.P.,  
Governor for Southern California

# ANNALS OF INTERNAL MEDICINE

VOLUME 21

SEPTEMBER, 1944

NUMBER 3

## TRAUMATIC NEUROSES IN COURT\*

By HUBERT WINSTON SMITH † and HARRY C. SOLOMON, ‡  
*Cambridge, Massachusetts*

### I. INTRODUCTION

WE can think of no more vexed or vexatious law-medicine problem than the proper appraisal and just compensation of so-called "traumatic neurosis."<sup>1</sup> Our intent is not to hack and hew, first with the scientific sword

\* Received for publication January 20, 1944.

Because of lack of space, it has been necessary to omit most of the numerous legal citations with which the manuscript was documented. Readers wishing to consult the original sources will find these references published in full in *Virginia Law Review*, 1943, xxx, 87.

† LL.B., M.D., Associate in Medical-Legal Research in the Harvard Law School and in the Department of Legal Medicine, Harvard Medical School (on leave of absence), now Lt. MC-V (S), USNR. This article was completed before entry into active service.

‡ M.D., Professor of Psychiatry, Harvard Medical School, and Director, Boston Psychopathic Hospital.

<sup>1</sup> As the Supreme Court of Washington said, "An allowance of damages in the cases of traumatic neurasthenia touches the border of speculation at best." *Mickelson v. Fischer*, 81 Wash. 423, 142 Pac. 1160 (1914).

Although medical literature has not neglected traumatic neurosis, very little seems to have been written regarding its legal implications. See TIBBETTS, F. V. W.: *Neurasthenia*, the result of nervous shock, as a ground for damages, *Cent. Law Jr.*, 1904, lix, 83. Some of the medical material is outmoded and many of the cases cited involve nervous shock, a physiological response, rather than traumatic neurosis which is a psychological reaction.

More recently, Stotter has put by question, without attempting to answer it, one of the salient legal problems posed by neurotic responses, namely: "In negligence cases, does mental pain and anguish include unconscious exaggeration of pain and all the host of mental ills that are often precipitated by any traumatic event cast upon one that is predisposed to mental illness? . . . Whether such mental pain and incapacity to function is the proximate result of a specific act on the part of someone else is quite hard to answer. There is always back of these cases a pre-disposition, a preëxisting cause. In the words of the psychiatrist such would be termed only a precipitating cause, real causes going back often to childhood experiences. The legal definition of proximate cause helps us but little and would no doubt be broad enough to cover what is meant in psychiatry by a precipitating cause." Having cracked the lid of this Pandora's box, the author closes it quickly, leaving it for others to open it full wide. He does not attempt to gather or to analyze the authorities.

STOTTER, R. O.: *Extent of liability for injuries to neurotic person yet to be decided*, *The State Bar Jr.*, Calif., 1941, xvi, 44.

The authors have published a version of this study for the legal profession buttressed with numerous citations of cases and certain special appendices which would only encumber a medical presentation. See *Virginia Law Review*, 1943, xxx, 87.

and then with the legal axe. We shall attempt, with some doubts, the more delicate and difficult task of weaving scientific and legal threads into a garment, albeit a Joseph's coat, which jurist, trial lawyer and expert witness may all wear with some degree of satisfaction.

A person who seeks compensation for traumatic neurosis must find some foundation for liability, and his legal claim will fall into one of the following categories:

1. A *tort* action for personal injury allegedly inflicted by the fault (negligent or intentional) of the defendant;
2. A *workmen's compensation claim* for disability allegedly due to an accidental injury received in the course and scope of employment;
3. A *war risk insurance claim* for total and permanent disability allegedly incurred before the insurance policy lapsed for non-payment of premiums;
4. A claim under a *life, health or accident insurance policy* by a person in civilian life.

## II. GENERAL CLINICAL CHARACTERIZATION OF THE NEUROSES

In a consideration of disease entities, one hopes to have a knowledge of etiology, pathology, or pathological physiology, a clear description of the symptoms and course of the disorder. These factors in complete form are not available in regard to those disorders which we designate as "psychoneuroses."

In a discussion of medical problems, as of all scientific matters, a clear definition of terms is usually a prerequisite. Unfortunately, it is not possible to define precisely the term "psychoneurosis." In fact, most textbooks baldly state that one can describe the symptoms of the psychoneuroses, divide them into symptomatic categories, but that one cannot either limit the territory of the disorders or tell where the psychoneurosis is to be separated from the normal. Such statements refer, naturally, to the borderline case, not to the full blown conditions of which we shall speak. Nor is it difficult for the experienced psychiatric examiner to spot the usual pre-neurotic constitution, if proper heed be paid to the individual's history and behavior patterns rather than solely to a search for an organic disease or lesion. It is fundamental to our concept that no structural pathologic lesion of the nervous or visceral systems has been discovered or indeed exists to explain the psychoneuroses. This viewpoint has certain consequences. It places the psychoneuroses in a different compartment from most diseases; it does not allow for a check of diagnosis through studies of pathology. A second fundamental concept is that the disorder or disorders are chiefly manifest in the mental life of the sufferer and, therefore, largely subjective, although many of the symptoms have organic or objective components. This second principle has led to the conception of the etiology of the psychoneuroses as in the field of the psyche, and one usually considers the cause as psychogenic.

Summing up the foregoing, it may be said that the psychoneuroses represent a group of symptom complexes or syndromes having no structural lesion, arising psychogenetically or out of the stresses and experiences of life, and manifested largely by subjective feelings and thoughts with some secondary physiological deviations. One must also assume that some individuals are more able and some less able to withstand the stresses and vicissitudes of life. And so the concept of individual vulnerability is introduced, with the further implication of the stability of the constitutional equipment. This brings in another term difficult to define and to measure, but a factor which must be estimated and assigned a value, as we shall see later. One may well believe that no one can withstand certain severe stresses, and therefore vulnerability is a matter of degree of resistance. This means we must take the resistance of the average person, roughly estimated, as our norm in determining whether the supposedly causal stimulus would have been adequate to produce neurosis in an ordinary individual. Undoubtedly, training or conditioning increases or decreases the threshold of vulnerability. Or, one may even reverse the point of view and see in the psychoneurotic an individual with a talent or capacity for worry, fear, concern, and other emotional and thinking mechanisms, possibly paralleling the function of imagination, which can be developed to a very high degree. Whatever the point of view, it is necessary in our opinion to take into account the pre-traumatic personality for the purpose of discovering what part of the total injury really represents a preëxisting neurotic constitution merely expressing itself by more obvious symptoms in response to stimuli which would cause no such symptoms in a normally constituted person. The legal import of this concept is enormous. It means that persons who develop more patent forms of neurosis in response to traumatic stimuli inadequate so to injure a normal person, are not caused thereby to develop the neurosis as a new and original condition. It is legally erroneous and socially unjust to compensate them on any such theory. Such cases are properly to be regarded as instances of aggravation of preëxisting injuries or impairments, and so compensated modestly. The neurotic constitution is the major factor in the disability, and it antedates the particular exacerbation of symptoms for which the plaintiff seeks damages.

It may also be accepted as true that all individuals have some tendency or capacity to worry, to be fearful, to be concerned, and that all have some psychoneurotic manifestations. This is much like saying that no one is free of some fear of bodily disease, but not thereby ill. As psychoneurotic mechanisms are well-nigh universal, one needs some rule of thumb for making a diagnosis and evaluating the case under consideration. It is a general working principle that when symptoms impede the efficiency of an individual or make life pretty uncomfortable, the diagnosis may be justified. It must be remembered that there need be no parallelism between the severity of symptoms and the effectiveness of the individual. Many of the most efficient executives, researchers, teachers, physicians, and lawyers have marked psycho-

neurotic phobias, anxiety states, compulsions, and other symptoms. Nor is it possible to evaluate the amount of discomfort such symptoms engender. In fact, there is often a suspicion that they give satisfaction, if not pleasure. And in the literature and clinic, attention is given to the presumptive protective value of the symptoms, their use for gaining some purposeful end, or their value as safety valves.

As the result of contributions to the study of the psychoneuroses by Janet, and especially by Freud, it is generally conceded that the cause of psychoneurosis lies in emotional and mental conflicts which have not been adequately faced or resolved, and which have been pushed aside from the normal thinking processes of the individual. The distress caused by the inability properly to resolve such conflicts is supposed to give rise to various types of discomfort, and thus the symptoms represent a diffuse form of expression. Whereas this is the point of view held by the majority of students of this subject, there is another school of thought which sees in the psychoneurotic an individual with an organic defect in the form of a poorly knit or poorly constructed nervous system. The latter point of view lacks sufficient scientific substantiation and for this reason, at the present time, has relatively little support, although lip service is generally given to the statement that if and when more information comes to hand, the more psychological view may be modified.

As already stated, it is the usual custom to describe rather than define the psychoneuroses, and for purposes of exposition, this group of disorders is usually sub-divided into three or four categories, namely, hysteria, neurasthenia, anxiety states, and the compulsive, obsessive states. These categories are by no means mutually exclusive, but, on the contrary, the symptoms characteristic of each category are likely to be found in greater or less extent in a case falling in any group.

#### 1. Characterization of *hysteria*.

The main characteristic of hysteria is that symptoms are referable to the sensory-motor nervous system. Thus, the patient will present symptoms of paralysis, that is motor weakness, or changes in sensation. The hysterical patient may present paralysis of an extremity, of half of the body, or he may be unable to phonate and talk only in a whisper, or he may be unable to talk at all (aphasia). Convulsions similar to those seen in epilepsy may occur. In the sensory sphere, one meets patients showing areas of anesthesia, that is, inability to appreciate touch, pain, or temperature changes; total blindness, limitation of the field of vision, or double vision. The patient may be completely deaf, or show disorders of other special senses. Loss of memory (amnesia), double personalities, and symptoms of this type, are also classified as hysterical. In other words, those disorders not due to real changes within the nervous system, but giving symptoms similar to those found in true organic disease apparently arising from psychologic causes, form the group designated as hysteria.

## 2. Characterization of *neurasthenia*.

The neurasthenic group has as its main symptoms the complaint of weakness, sense of exhaustion, various pains, aches, and distress of a bodily nature, associated, as a rule, with concern about the functions of various organs. Frequently in cases of this group, one finds digestive distress, attacks of diarrhea, pain in the bladder with frequent desire to micturate, a feeling of pressure in the chest with concern about the state of the heart, headaches with fear of brain tumor, difficulty in concentration, disturbed sleep frequently resulting in a concern about sanity. With the preoccupation of the sufferer with his bodily sensations and functions, the pleasure in living is greatly reduced and a sense of futility and lack of interest occurs.

## 3. Characterization of *anxiety states*.

In the anxiety states, one finds an individual who becomes extremely panicky on occasions, usually without any understanding of the reason for this panic. These attacks are likely to be of relatively short duration, but represent real states of tremendous agitation. Such states of necessity are accompanied by the physical component of acute fright, namely, rapid pulse, strongly beating heart, tremors, cold perspiration, and a sense of impending collapse. These physical signs, which are part of fear and panic, naturally lead the patient to have concern about his viscera.

## 4. Characterization of *obsessive compulsive syndrome*.

The obsessive compulsive syndrome is manifested by the patient having the idea that he is compelled or is likely to be compelled to carry out acts which are contrary to his ordinary desires. Thus, in the compulsive syndrome, the individual may be greatly distressed because he feels that he will throw himself out of a window, that he will harm his child, that he will run some one down by automobile. The obsessive states are those in which the individual has thoughts running through his mind which he feels unable to control or put aside. Sometimes these will be in the form of indecent expressions or licentious ideas and mind pictures. The individual will usually say that it is much like a tune running through one's mind of which one cannot get rid. Because of unpleasant connotations, those thoughts or pictures interrupt the ordinary flow of thinking and become extremely distressing. In this category one also usually considers the phobias or fears, such as the fear of crossing the street or being in closed places, the fear of riding on a street car or train, or going more than a short distance from home, the fear of high places. These fears, which the individual will agree are unreasonable and contrary to his better judgment, nevertheless lead to a sense of panic if he tries to do the thing which produces the fear.<sup>2</sup>

<sup>2</sup> P, a 23 year old graduate of McGill University in electrical engineering, decided to gain experience by working for a time as a lineman. D's employees failed to cut off the power from a line on which he was working. An electrical current leaped with a spark or a flash from a wire 4 inches away, which carried 16,000 volts, and went through his body, entering at one of his hands, and going out at one of his feet. It was not possible to show how much electricity actually leaped from the high tension line, but apparently he was not so much injured as terrified. P developed mixed symptoms of neurasthenia and hysteria,



As one might anticipate, the compulsive syndrome is rarely the basis of claim in traumatic neurosis, but obsessive states about the permanence of disability and fears for family are commonly linked with general anxiety reactions in the neuroses of injured workmen.

The reader will have observed that all these symptoms and symptom-complexes, except those of the hysterical states, are primarily subjective. It is what the individual thinks and feels or fears that is important. In so far as these subjective feelings interfere with normal living, working, and playing, in so far are they serious and disabling. The objective evaluation can be made only by watching the behavior of the individual. If the phobic never leaves his room because of the state of fear and panic such an attempt produces, one must conclude that it has disturbed the entire tenor of his life.

*Necessity for Distinguishing Residual Symptoms of Traumatic Injury to the Brain from Similar Symptoms of Psychoneuroses.*

Accepting the foregoing postulates concerning the psychoneuroses, it follows that symptoms arising as the result of organic brain injury due to trauma are not properly considered as psychoneuroses. Whether the traumatic brain injury is in the form of cerebral concussion, hemorrhage, or contusion does not alter this statement. Therefore, disorders of this type are not in the scope of this discussion, except in the form of differential diagnosis in order that they may be excluded.

Symptoms arising from traumatic brain damage often have a remarkable similarity to those of a true psychoneurosis, and are distinguishable chiefly by objective evidences of real organic brain changes. Such evidences are protracted periods of unconsciousness; blood in the cerebrospinal fluid and increased intracranial pressure, both discoverable by the virtually riskless diagnostic expedient of lumbar puncture; changes in the reflexes; motor weakness and sensory changes of specific neurological variety; and mental changes that can be directly associated with disorder of brain structure. In many instances, the decision as to whether symptoms are the result of traumatic effort or are of a psychoneurotic nature is a matter of judgment rather than a matter of definite objective differentiation. In addition, it frequently happens that there is a combination of the effects of organic brain disturbances and psychoneurotic symptomatology. The latter may at times mask the former.

As the effects of traumatic injury of the brain recede, psychoneurotic manifestations may take the foreground among the presenting symptoms. These factors produce difficult practical problems of decision, but do not affect the underlying theoretical concepts about the psychoneuroses.

If one accepts the point of view that the psychoneuroses are of purely psychological cause and nature, and if they are to be considered as the result

in part manifested by temporary paralysis followed by involuntary twitching and shaking of his muscles, and by a deep rooted dread and fear of electricity which presented a serious obstacle to pursuit of his chosen profession. Verdict and judgment for P for \$7,500, affirmed on appeal. *Summerskill v. Vermont Power and Mfg. Co.*, 91 Vt. 251, 99 Atl. 1017 (1917).

of unresolved conflicts, it is in order to ask how a trauma to the head or some other part of the body can be causally related to the appearance of neurotic symptoms. Obviously, the relationship is not a direct one, and is not dependent upon the force or nature of the physical impact, but rather, any relationship present is an indirect one in which the trauma affords the optimum conditions for the outbreak of symptoms.

Perhaps this can best be illustrated by reference to the war neuroses, as is essentially described in the literature of both World Wars. Following partial burial or concussive effects of near-by explosions, many individuals developed psychoneurotic states of the various sub-divisions of this disorder. The formulation runs somewhat as follows. A soldier, worried, anxious, frightened, and fatigued by the conditions of warfare, is faced by the conflict between the instinct of self-preservation and the desire to do his job faithfully and well. A minor concussion or other accident following an explosion leading to removal to a medical installation affords an opportunity through unconscious mechanisms for the development of symptoms, the continuance of which lead to removal from the front and care in hospital. Thus, the symptoms solve the man's immediate problem. It is assumed that this does not occur through conscious planning but rather occurs in part spontaneously, and in part by suggestion, and therefore cannot be considered as malingering. The accident or trauma could then be considered as the opportune moment for the development of symptoms which the psychological conflicts and the personality structure of the individual had made possible. A similar mechanism can be readily conceived as operating in the case of superficial traumatic injury sustained in civilian life, substituting only other forms of conflict and discontent for those existing in the war situation. Among the conflicting emotions and desires, fears and worries, and anxieties existing in ordinary civilian circumstances, one considers discontent with a job, fear of losing one's income, unsatisfactory marital relations, lack of good social adjustments, and almost any variety of maladjustment. An accident, whether it be to the head or other part of the body, may then break down the individual's resistance and allow the psychoneurotic mechanisms to have full sway. When an injury to the head has occurred, several factors arise which in themselves are important in the causation and prolongation of symptoms. For example, an individual may be fearful that a blow to his head has damaged his brain, and the result of such fear, with the associated idea of being unable to work and support himself and his family, can be productive of symptoms. Discontent with the type of job at which the accident occurred, fear of discharge if he returns to work and is not entirely competent either because of general inability or because of lessened capacity resulting from the injury may cause psychoneurotic manifestations.

The symptoms arising in this fashion, associated as they so frequently are with the question of compensation, often evoke the suspicion that the injured individual is consciously producing or exaggerating his symptoms for

financial gain. As already frequently stated in this discussion, there is no method of accurately measuring the intensity of the complaints described by the injured person. These facts raise special problems of evaluation in fixing a just compensation, in cases where it is due, and we shall advert to them at a subsequent point in this paper.

### III. SPECIFIC LAW-MEDICINE PROBLEMS PRESENTED BY TRAUMATIC NEUROSIS

*A. The Law of Torts. Assuming there has been an impact produced by defendant, to what extent shall the law protect the idiosyncratic or excessively vulnerable person in allowing him damages?*

Assume for the moment that study of the claimant's pre-traumatic personality shows a neurotic constitution or condition sufficient to make the subject an extreme reactor to stimuli which would only mildly affect the average person, if at all. In his case a \$5.00 touch may become a \$10,000 disability. Shall the law protect this fragile fellow to the full, or where shall legal and social policy draw the lines limiting the compensation he may obtain?

This is one of the most intriguing problems to be found in the realm of law, for it plumbs legal theory and the philosophy of social justice. One is aided in coming to just conclusions by remembering the essential ingredients of the trial formula:

$$\begin{array}{c} \text{Duty} \rightarrow \text{Dereliction} \rightarrow \text{Proximate Causation} \rightarrow \text{Injury} \parallel \leftarrow \text{Defenses} \\ \text{(Plaintiff or claimant must prove)} \qquad \qquad \qquad \parallel \text{(Defendant must prove)} \end{array}$$

Any plaintiff or claimant who seeks money compensation for alleged injury, in order to establish a *prima facie* case of liability adequate to get his claim to the jury or to sustain a verdict, has the burden of proof to show by substantial evidence the concurrent existence of duty, dereliction, direct causation and damages. If he fails to do so, the court, on motion timely made by the defendant, must instruct the jury to return a verdict for the defendant. The limits of liability for injuries ascribed to psychic stimuli have been discussed elsewhere.<sup>3</sup> It seems clear that a defendant commits no dereliction if he indulges conduct which would not injure a normally constituted person, even though it actually does harm an idiosyncratic individual, P (plaintiff). This rule is subject to the assumption that the actor cannot be charged with notice of the unusual risk and does not intend or desire to injure.<sup>3</sup> Here D escapes liability on the ground that P cannot prove his conduct culpable, and this negatives any primary liability.

In the majority of traumatic neurosis cases, there is usually some minor impact and superficial injury, inadequate to cause neurosis on a traumatic

<sup>3</sup> SMITH, H. W., and COBB, S.: Tort liability for psychic stimuli, in SMITH on Scientific Proof and Relations of Law and Medicine, 1944, Matthew-Bender and Co., Albany, N. Y., Vol. 1 (in press).

basis, but sufficient to found a primary liability. The question is not now one of culpability or no culpability, liability or not, but whether, and in what way, idiosyncrasy may be proved by a defendant to limit the damages he must pay. Both British<sup>4</sup> and American courts,<sup>5</sup> with a singular unanimity,

<sup>4</sup> This doctrine was expressed in *Dulieu v. White & Sons* (Eng.), 2 K.B. 669 (1901), 70 L.J. (1901) K.B. Div. 837, one of the historic precedents on legal liability for psychic stimuli. P alleged that on July 20, 1900, she was pregnant but was working behind the bar of her husband's public house, when D negligently drove a pair horse van into the tavern allegedly frightening her so badly that she suffered nervous shock and a consequent miscarriage. Justice Kennedy in ruling on a demurrer held the injury actionable. He rejected defendant's contention that the plaintiff's unknown vulnerability would defeat liability, saying: "It may be admitted that the plaintiff, as regards the personal injuries, would not have suffered exactly as she did, and probably not to the same extent as she did, if she had not been pregnant at the time; and no doubt the driver of the defendant's horses could not anticipate that she was in this condition. But what does that fact matter? If a man is negligently run over or otherwise negligently injured, it is no answer to the sufferer's claim for damages that he would have suffered less injury, or no injury at all, if he had not had an unusually thin skull or an unusually weak heart."

In the *Dulieu* case, the conduct was negligent when tested by risk of injury to an average person, and accordingly the question was not one of primary liability, but whether P's unknown vulnerability would limit the damages recoverable. In *Owens v. Liverpool Corp.* (Eng.), 1 K.B. 394 (1937), MacKinnon, L. J. failed to perceive this crucial distinction. He seemed willing to apply the doctrine to raise a primary liability for a purely idiosyncratic response. This was an extension not warranted by British precedents or by prevailing concepts of tort law as to what constitutes culpable conduct sufficient to make a defendant liable.

<sup>5</sup> In American law two cases may be regarded as "stem" authorities. In each case it was clear from the facts and the court's doctrinal approach that defendant's conduct was such as to create a primary liability to a plaintiff possessed of average health. The vital holding was that the defendant could not have his damages reduced by proving that plaintiff's unknown idiosyncrasy caused his injury to exceed that which a person possessed of average health would have sustained.

*Purcell v. St. Paul City R. Co.*, 48 Minn. 134, 50 N.W. 1034 (1892), 16 L.R.A. 203; *Spade v. Lynn & Boston Railroad*, 172 Mass. 488, 52 N.E. 747 (1899), 43 L.R.A. 832, 70 Am. St. Rep. 298, 5 Am. Neg. Rep. 367, 11 A.L.R. 1124. Such is the rule generally followed by American jurisdictions. The main difference in judicial approach lies in the varying vigilance which courts show in excluding preëxisting impairments from compensation. Authorities are collected in the Digest System under Damages, Keys 33, 95, 132(3), 168, and 208(2).

What part of plaintiff's injury represents compensable aggravation, and what part non-compensable poor health antedating the accident requires most careful discrimination by jury and judge if awards are to be kept at just levels.

*Flood v. Smith*, 126 Conn. 644, 13 A.(2d) 677 (1940), illustrates this problem of separating non-compensable from compensable factors. As the result of an automobile collision caused by negligence of D, P<sub>1</sub> and P<sub>2</sub> sustained injuries more excessive than an average person would have suffered from a like stimulus. Proof showed that two years before, P<sub>1</sub>, a 28 year old man, was hurt in an automobile accident, suffering a fracture of the skull and injury of his nervous system, from which he made a substantial interim recovery. P<sub>2</sub>, his companion, was a 70 year old library cataloguer. Her medical history revealed that prior to the accident, she had undergone two nervous breakdowns and the surgical removal of a cancerous breast. In the instant accident P<sub>1</sub> and P<sub>2</sub> sustained bruises and suffered extreme nervous shock, in P<sub>2</sub>'s case aggravated by her morbid fears that a blow received at the site of her amputated breast would reactivate her cancer. The jury awarded P<sub>1</sub> \$3,500 and P<sub>2</sub> \$4,000. The trial court thought these damages were excessive. It therefore granted D's motion for a new trial unless P<sub>1</sub>, by remittitur, should relinquish \$1,275 of the verdict, and P<sub>2</sub> \$2,027. P<sub>1</sub> and P<sub>2</sub> appealed. Held: The damages awarded by the jury were not excessive. Case remanded with orders for trial court to enter judgment for the full verdicts. The Connecticut Supreme Court said, "The plaintiffs are entitled to recover full compensation for all damage proximately resulting from the defendant's negligence, even though their injuries are more serious than they would otherwise have been because of preëxisting physical or nervous conditions." This statement of legal doctrine expresses the majority view, but it glosses over the clinical certainty in such cases that part of the post-accident symptoms are due to pre-accident causes and do not represent aggravation by the accident.

have held that once a defendant can be culpably connected with the general type of injury he has caused the plaintiff to suffer, the bars are down. The defendant cannot then be heard to say: "I should not be held to pay for the full harm but only for the degree of injury which a normally constituted person would suffer." The concept is sometimes pithily stated that a tortfeasor takes his victim as he finds him. As between the culpable actor and the innocent subject who is injured, there is equity in placing the loss on the former.

Over enthusiasm for this cliché has led some courts to the erroneous conclusion that once culpability can be proved so as to create a primary right of action, the defendant is liable for all consequences actually caused by his wrongful conduct. The better view, however, is that remoteness of expectation of injury runs both to culpability and to compensation. There is an independent doctrine of remoteness of damages, whose exact limits are still in process of being fixed. Its cardinal principle is that no harm actually suffered is compensable if it falls outside the risk of the defendant's conduct. Damages may be remote for three reasons:

(1) Following upon defendant's conduct there may be a new and intervening cause which stands in closer (or, as some say, more proximate) relationship to the final injury.<sup>6</sup> This involves a defect in proof of one term of the liability formula.

<sup>6</sup> Assume that D's conduct results in a superficial physical injury to P. D cannot be held liable in damages for independently caused sequelae, as, for instance:

(1) *If subsequent to the accident, P begins worrying about what might have happened to him and in that event to his family, thereby developing an anxiety neurosis.*

In *Phelps Dodge Corporation v. Industrial Commission*, 46 Ariz. 162, 49 P.(2d) 391 (1935), the facts were that X, a miner, ran 500 feet to reach fresh air after blast of a "missed hole" caused shafts and drifts of the sulphide ore mine to become filled up with smoke, sulphur gas and dust. He suffered no injury but thereafter developed a neurosis from brooding over what might have happened to him, and in that event what would have been the lot of his family. Held, since the neurosis was not caused by nervous shock produced by the episode, but by subsequent brooding, the neurosis was not result of an injury sustained by accidental means, and was not compensable under terms of the Arizona Compensation Act.

(2) *If as the result of such brooding P is led to commit suicide:*

In certain interesting cases claim has been made under Workmen's Compensation Acts for suicide due to insanity allegedly caused by an accidental injury received in course of employment. Courts have held it is not enough that insanity was indirectly caused by the injury if the more immediate cause was worrying and fear of losing employment (*Grime v. Fletcher* (Eng. 1915), 1 King's Bench 734; 8 B.W.C.C. 11, C.A.) or depression and brooding over inability to work (*Withers v. London, Brighton and South Coast Rail Co.* (Eng. 1916), 2 King's Bench 772, 9 B.W.C.C. 616, C.A.). So, also, there is a defect in causal connection where decedent's preparation showed a "moderately intelligent mental power which knew the purpose and physical effect of the suicidal act." *Kazazian v. Segan*, 14 N.J. Misc. 78, 182 Atl. 351 (1938).

In the type case mentioned under (1) and (2) *supra*, there may be *actual causation*, but it must be admitted that lapse of time, the entry of independent causes, and difficulties of proof, justify the law in drawing a boundary line of liability, though somewhat arbitrarily, to mark off and exclude the morass of speculation.

(3) *Where the disability has arisen from anxiety, worry or brooding over the proceedings for compensation, or has arisen from a cause unrelated to the accident itself, there is no right of compensation.*

*A mental state or nervous disturbance caused merely by pendency of compensation proceedings is even less necessarily referable to the injury.*

(2) The injury, in type, would be remote in expectation of the prudent actor.<sup>7</sup> This involves a defect in proof of one term of the liability formula, namely *derelection*.

(3) The particular injury may not be remote in expectation, and no logical reason may exist for its exclusion under the four terms of the liability formula, yet courts may deny compensation on grounds of extrinsic policy. Such considerations constitute arbitrary restrictions on the damages recoverable. Usually they find their justification in difficulties of proof, or in judicial aversion to making the load of liability inordinately heavy.<sup>8</sup>

*Coffey v. Coffey Laundries, Inc.*, 108 Conn. 493, 143 Atl. 880 (1928).

Where the accidental injury involves a substantial stimulus which directly causes the neurosis, without delay, the case is different: here there is no defect in causation and no question about liability. Thus, where claimant developed an anxiety neurosis due to fear and anxiety about a hole in his skull produced by injury and operation, this neurosis was properly held to be compensable. *National Lumber & Creosoting Co. v. Kelly*, — Colo. —, 75 P.(2d) 144 (1938).

*Deliberate and unnecessary exposure of oneself to injury, even if remotely occasioned by D's conduct, may constitute the immediate cause of harm suffered and bar recovery of damages.*

D, excavating adjoining land, impaired the lateral support of P's hotel. P was warned that guests should be cleared from the imperiled wing. P did this, and after waiting for two hours, labored strenuously, and unnecessarily, in helping to move her furniture out. She alleged that fright drove her to this overexertion and that the latter caused a nervous breakdown. Verdict and judgment for P for \$2,000. On appeal, reversed: there was a break in proximate causation, for P did not act spontaneously in response to fright or to escape an immediate emergency. Her injury was caused by her independent, deliberate acts.

*Cherry v. General Petroleum Corporation*, 172 Wash. 688, 21 P.(2d) 520 (1933).

<sup>7</sup> Here the injury is outside the risk of defendant's conduct. Assume that D, hurrying to a foot-ball game through a large crowd, carelessly brushes P aside, the impact being enough to inflict a superficial wound. P is a hemophiliac and bleeds to death from a scratch thus received. Or suppose P has the unusual disease *fragilitas ossium*, a rare congenital weakness of bones characterized by multiple fractures which occur spontaneously or upon moderate jolting. As a result of D's impact, P's bones break in several places. In these cases D may be held responsible for nominal damages if he is negligent, but he can hardly be taxed with liability for the full injury. This is true because the result is not a mere exaggeration of a foreseeable harm, but belongs to a category of consequences entirely beyond any foreseeable risk of injury involved in D's conduct.

Again, suppose that D negligently collides with P's car, so wounding P that the latter must go into hospital for treatment. Without any notice of their incompetency, P accepts treatment from the hospital physicians, and suffers further injury as a result of their negligent ministrations. P can hold D liable in damages for both his original injury and for the effects of the malpractice.

The authorities are collected in 8 A.L.R. 506, 39 A.L.R. 1268, and 126 A.L.R. 912.

Assume instead, that P's further injury is not due to medical malpractice but to lightning striking the ward in which he is confined. P cannot hold D in damages for this additional injury. D's conduct in injuring P created a new risk that the latter would come under medical care and have his wounds aggravated by negligent treatment. That D's conduct was calculated to send P into the hospital did not, however, involve a foreseeable risk that P would be struck by lightning, nor did it increase the probability of such an injury.

In *Denison, B. & N.O.R. Co. v. Barry*, 98 Tex. 248, 82 S.W. 5 (1904) reversing (Tex. Civ. App.) 80 S.W. 634 (1904), defendant railroad negligently constructed a dump in such way as to throw water back on P's home. P's wife was pregnant. As the water rose up to the floor of the house she became frightened at the prospect of drowning and fled with her husband to a safe place. This episode caused P's wife to suffer a threatened miscarriage involving pain and sickness of several weeks' duration. D was unaware that P's wife was pregnant. The Texas Supreme Court in reforming a judgment obtained by P in the trial court, upheld the sum awarded for property damage, but denied any right for compensation for the wife's physical illness on the ground that this injury was too remote a consequence to be anticipated by the actor.

<sup>8</sup> One who causes a violent collision can foresee that a scene of horror will be created which may cause involved persons such as the plaintiff, who behold the spectacle, to suffer

We may hope and expect to see fuller and more effective use made of this doctrine of remoteness of damages. A bold court would be warranted in holding that the development of neurosis following a minimal impact is an idiosyncratic response, in which cause-effect relationships are hopelessly obscured, and that difficulties of proof, appraisal and just compensation are so great as to raise an extrinsic policy against their redress.<sup>9</sup> All the logical grounds for holding a particular item of damages remote, while recognizing a primary liability for the impact, and any nervous shock, could be validly invoked.

Courts timid about thus cutting off entirely the liability for neurosis caused by stimuli too insubstantial and inadequate to so injure the average person, may limit the measure of damages by resorting to another principle. It is the rule everywhere that a plaintiff afflicted with a preëxisting illness or impairment, cannot hold one who injures him liable in damages for his prior condition, but only for its aggravation.<sup>10</sup> It is good logic and settled law that a defendant is not liable for an injury, or any part thereof, which he did not cause. Now traumatic neurosis cases yield nicely to separation into three classes:

(1) A very large group where a stimulus, psychic or traumatic, patently inadequate so to affect an average person, causes the plaintiff to develop neurosis. These cases are all presumptively instances of an idiosyncratic response. They bespeak a pre-neurotic personality, and a competent psychiatrist could usually expose evidence of definite personality neurosis antedating the allegedly causal episode.

nervous shock. Liability exists for nervous shock or injury due to such immediate psychic stimuli.

The defendant also can foresee that persons going away from the scene of a railroad wreck may suffer secondary shock from beholding the wounds of fellow passengers, but damages are not allowed for this more distant consequence.

Nor will the courts allow damages for nervous shock and consequent injury caused in a parent, not present within the circle of risk, but induced by secondary reports that her child has been injured or killed through defendant's negligence.

So, too, it is a most natural and foreseeable consequence of injuring a minor, that his parents will suffer mental anguish and nervous shock from discovering his injury or maimed condition, or through sympathy for his deformity, but the law refuses to hold the defendant answerable in damages for such results.

A pregnant woman who is injured through defendant's negligence may recover damages for mental anguish due to her reasonable fears that the child will be born deformed, but if she suffers a traumatic miscarriage she can recover no damages for death of the child, or for mental anguish caused thereby; nor can she recover damages for mental anguish caused from beholding traumatic deformities in a living child after it is born.

<sup>9</sup> In particular cases, these considerations may warrant a refusal to recognize any *actual causation*, especially if the stimulus is trivial and the symptom-free time interval long. *Stanford v. Longe & Wolfe* (La. App.), 199 So. 608 (1941); *The Rigel* (Eng.-Admiralty) (1912) P. 99. And see *Cookson v. Barber Co.*, 120 Me. 527, 115 Atl. 285 (1921).

An able neuropsychiatrist of our acquaintance went so far as to say it would be a signal service if courts could be induced to deny compensation in *all* cases of traumatic neurosis, as this would do more than any medical means to banish the disorder. We would not go so far as to espouse universal denial of compensation, but certainly this point of view has much in its favor in regard to neuroses which appear following trivial stimuli.

<sup>10</sup> This rule is axiomatic. Defendant is entitled to have the jury instructed, in proper cases, that it is for them to consider plaintiff's previous physical condition in determining whether P's nervous symptoms were or were not consequences of general ill health.

(2) At the other extreme we have a smaller group of cases, where the plaintiff has sustained severe associated injuries or is led by mode of treatment to the reasonable belief that he has a serious and permanent disability, or is subjected to a harrowing psychic stimulus of a kind not readily effaced from the mind. The development of neurosis in these cases is not presumptively idiosyncratic, but each case must be judged on its own merit after proper medical examination.

(3) A middle group, seemingly the smallest of all, contains border-line cases falling between groups (1) and (2). This group tends to diminish in size as we gain increasing insight into the neuroses and as the cases investigated are studied by competent psychiatrists.

Thus, though we do not know all there is to be learned about the neuroses, it is feasible, with a nearer approach to exact justice, to sort the cases into these three main groups for purposes of making a just appraisal and evaluation of a particular case. We have applied this technic in surveying all the traumatic neurosis cases, as far as we could find them, which have reached appeal courts of the British Empire and of the United States. We find that three-fourths of them fall without question in the group of idiosyncratic response to trivial stimuli. Yet it is precisely in this group that lack of proper information causes juries and courts to allow extravagant awards.

This disturbing phenomenon would soon be corrected if triers of fact and appeal judges realized that the neurotic who presents a deplorable spectacle in court, was not immediately before the accident truly "as fit as a fiddle" or "the strongest woman in the house" or "the picture of health." A plaintiff can always bring trusting neighbors to court bearing witness to his hale and hearty pre-accident health, and ready to describe calamitous changes noticed in him shortly after receipt of the trivial impact. These laymen see only the flowering stalk of the neurosis, not the extensive roots underground, nor how the trivial stimulus, like a little rain water, combines, with the sun's warmth and other environmental factors, to cause rapid surface growth. Actually, as we shall continue to stress, the trivial stimulus which causes appearance of new symptoms (or the flowering stalk of the neurosis) merely adds to a process already underway.

If we may shift metaphors, another fit analogy is to compare the waxing of this type of traumatic neurosis to the breaking open of an old scar, which has healed, only to break open at a later date in response to some trivial stress or some purposeful need of the individual.

Still again, we may compare the pre-traumatic condition of such a neurotic to a cracked vase. The unobservant or untrained eye may not notice the crack, but only that the vase will hold water. It is only when the crack spreads and the vase will no longer hold water that he is conscious of any defect. But the law of torts must follow the rule of the market place and take cognizance that a cracked vase is not so valuable as an intact one. If the defendant's conduct causes the crack to spread, he may justly insist that he shall not make compensation on any assumption that the vase was previ-



ously perfect. So here, traumatic neurosis resulting from trivial stimuli should be treated as mere accession to, or aggravation of, a preëxisting impairment.<sup>11</sup> Once this truth is grasped we can expect to see the measure of damages lowered to more modest levels.

#### IV. CHARACTERIZATION OF TRAUMATIC NEUROSIS LITIGATION

Who are the plaintiffs and who the defendants in this type of litigation? In analyzing those cases of traumatic neurosis which reached the appeal courts of the British Empire and of the United States, we divided them into two main classes as follows:

A. Cases of traumatic neurosis following trivial impact or psychic stimuli<sup>12</sup>;

B. Cases of traumatic neurosis incident to serious physical injuries.

We found that less than 3/8 of all the appeal cases fell in group B, despite the great numbers of serious personal injuries which fill the courts in modern times. Doubtless some of the 3/8 group were not neurosis cases but examples of neurotic-like symptoms following actual organic injury to the brain. Thus, more than 5/8 of all cases fell in group A. This conforms with clinical observations that most neurosis occurs on a "neurotic" or purely psychological basis.

In group B, involving traumatic neurosis incident to serious physical injuries, 43.5 per cent of cases were males, and 56.5 per cent females. In group A, containing traumatic neurosis following trivial impact or psychic stimuli, 27.1 per cent of cases were males and 72.9 per cent females. This finding further accentuates basic differences between the two groups of cases, and throws light upon the psychological mechanisms involved. Males venture into places of peril as much as females and so are as frequently exposed to the group A stimuli. But the male is usually the breadwinner; his thoughts are distracted from his experience by the tasks of his job, and further, he has much to lose and little to gain by developing a neurosis. The female is usually at home, has more time to ponder upon the experience, and more to gain and less to lose from developing symptoms. The independent post-accident psychological forces conducing to neurosis are apt to be more potent in her case.

It is noteworthy that more than 90 per cent of the defendants are healthy corporations, for the most part sturdy public utilities symbolic of wealth and

<sup>11</sup> This principle is so fundamental that it is above the vagaries of conflicting evidence, or defects in technical proof: we regard it as a scientific axiom entitled to recognition under the doctrine of judicial notice.

Some courts already have progressed part way to this goal, in reducing verdicts as excessive where the jury has allowed full damages despite evidence of plaintiff's preëxisting neurotic state or symptoms.

<sup>12</sup> Of 129 cases in 13 only could we say that the stimulus was such that it *might* have sufficed to cause neurosis in an average person.

Of these 13 cases, in three the neurosis was not due to the initial stimulus but to fears of permanent injury aroused by the manner in which the attending physician treated the case.

the ability to pay. The purposeful mechanisms of neurosis may operate on a sub-conscious level, but the hope of being compensated thrives best when a stout corporation can be looked to as the party defendant. There is reason to believe that one does not develop a neurosis so readily if the wrong is done by one's neighbor.

We were particularly impressed by the inadequacy of the stimulus in most of the group A cases (5/8 of all traumatic neurosis) to cause a neurosis in an average person. This finding substantiated our impressions that in most cases of traumatic neurosis, the alleged stimulus is only a trigger mechanism, and not the substantial cause of the neurosis.

Lastly, our analysis disclosed that group A cases of pure neurosis are being compensated almost as liberally as the group B cases. In the group A cases, the average jury verdict was for damages of \$8,317.20, and the average judgment entered by the appeal court was for \$6,037.29. In the group B cases, the average verdict awarded was for \$9,655.96, and the average judgment entered by the appeal court amounted to \$8,058.72. That the same range of compensation should be awarded in the two series is startling when we consider that the group B cases involve serious physical injuries, often permanent injury to the brain. Our finding in this respect shows that juries and courts have an exaggerated notion of the nature and permanence of traumatic neurosis following upon trivial stimuli.

#### V. APPLIED PROBLEMS OF PROOF IN ARRIVING AT A JUST RESULT IN TRAUMATIC NEUROSIIS CASES

Medical science recognizes that genuine traumatic neurosis can occur, that it can cause disability through psychological mechanisms which lead the subject to fixed beliefs that his health is impaired, and that it follows symptom patterns which permit diagnosis. British and American courts have accepted the medical concept that traumatic neurosis is a real injury, and so *prima facie* compensable in damages if the claimant further proves existence of duty, dereliction and direct causation. The vexatious problem has been how to appraise causation and how to arrive at a fair award of damages. There is no single cause for all the symptoms of such a neurosis and the sorting out of compensable injury is obscured by a variety of circumstances. We intend to explore the pervasive problems and the special ones which arise in the litigation of:

- a. Tort actions based on ordinary negligence;
- b. Workmen's Compensation cases;
- c. War Risk Insurance cases.

##### A. *Tort Litigation.*

##### 1. The Dramatic Appeal.

Psychological reactions aroused in the trier of fact play a dominant rôle in the making of proof. Traumatic neurosis, with its absence of organic

injury, might engender distrust and skepticism leading jurors to return small verdicts. On the other hand, the pitiable appearance of certain neurotics conduces to arouse sympathy and to swell damages. A female plaintiff is more able to capitalize on such sympathy reactions than a male.<sup>13</sup> For a proper female the court room may become a special stage for the enactment of a drama calculated to overthrow jury conservatism. Examples might be multiplied, but Judge Ulman's description of trial of such a case in his court illustrates at once the force and tempo which such a presentation may attain and the impact it may produce upon an attentive jury.<sup>14</sup>

*Case Summary.* Plaintiff, an actress known on the vaudeville and concert stage as "The Sweet Singer of the South," was playing an engagement in a Baltimore theater in the year 1928. Through negligence of defendant's stage hands in manipulating the "scrim-drop," a curtain made of tightly stretched gauze and weighted at the bottom with lengths of iron pipe, it became fouled and ripped open, releasing a long length of pipe. The pipe toppled toward plaintiff, and though a fellow actor caught the main weight on his arm, the upper end of the pipe in falling to the floor brushed by plaintiff's head and neck and struck her on one ankle. No one could say with assurance that it actually did come in contact with her head.

Plaintiff swooned and almost fell, was carried into the dressing room where she remained in a comatose condition for half an hour and then was taken to her hotel and put to bed. A physician who then examined her could find no evidence that P had been struck or injured about her head or neck. He did observe that P was extremely nervous and that she complained of great pain in those regions. This physician saw her daily until she departed for New York toward the end of the same week. According to the evidence, P became progressively worse, lost her ability to speak, and became paralyzed on her right side. She returned to her home in Alabama where she was completely bed-ridden for two months and thereafter used crutches to accomplish limited locomotion.

In the meantime, P had filed suit against the theater and the case came on for trial 18 months after the date of the initial episode. P's father, a Southern gentleman, a judge from Alabama, recounted impressively the story of his daughter's girlhood, her education at school and college and her vocal studies in New York. Kodak pictures were offered in evidence, showing P as she appeared before the accident, a wholesome-looking girl standing under the trees on the lawn of her Southern home. Other witnesses described her vocal studies and professional success, imparting to the attentive jurors "a picture of a beautiful young woman, with a lovely voice, a great career in concert and opera opening before her, and an assured income of about twelve thousand dollars a year." At this juncture, two days after the trial began, P was called to the stand. "With difficulty she rose from her seat. Her dignified, elderly father held her on one side, her aunt on the other. They placed her crutches beneath her arms. With their help she walked slowly across the court room, dragging her right leg, and sank, exhausted, into the witness chair." P was a prize exhibit in her own behalf; she appeared on the stand as a hopeless invalid, much aged in appearance, with professional hopes and normal life blasted. In testifying, her voice would fade into a whisper after the utterance of a few words. When this occurred, P would move her left hand gently to the right side of her throat, and press firmly against it as though to move some obstruction inside. "Then she paused a moment; and when she began to speak, her voice was strong and vibrant. But only for a few

<sup>13</sup> In the cases studied juries awarded males verdicts averaging \$7,198.23; in comparison, they awarded females verdicts averaging \$8,801.09.

<sup>14</sup> Ulman, J. A.: A judge takes the stand, 1933, Alfred A. Knopf, New York.

seconds; and the painful cycle was repeated. Among other things, she told the jury about the phonograph records she had made and sold to one of the great companies that market them."

To demonstrate the character of P's voice as it was before the accident, P's attorneys were permitted to play in the court room a phonograph record she had made. "I was never more surprised. The selection was a sentimental ballad of the music halls. The phonograph was a cheap one. I expected to hear that half throaty, half nasal voice which one associates with the vaudeville stage. Instead, the softer parts of the song were produced in a sweet, round voice, full of gentle sentiment; and the high notes were sung *bravura* in a manner that would reflect credit upon some of the best song recitalists I have ever heard. The court room was tense. As the notes of the song rang out full and clear, the plaintiff sat huddled in the witness chair with her handkerchief to her eyes, weeping silently. Then she left the stand on her crutches, dragging her right leg. She was still weeping when she took her seat on the front bench beside her dignified old father from Alabama." Medical experts called by plaintiff and by defendant agreed that P had no organic injury, that her complaints manifested traumatic neurosis and existed only on a psychological basis. D's witnesses related how closest physical examination by specialists showed no physical disease. It was on prognosis that medical opinion diverged sharply: P's witnesses thought that termination of the litigation would help her condition somewhat but that she would never be able to face an audience and sing again from a concert stage. D's witnesses foresaw a complete cure in six months or a year and no reason why she should not get well enough to continue her career as though nothing had interrupted it.

"When the case was tried, the plaintiff had lost already about eighteen months from her work. Before the accident she had earned about \$1,000 a month. Her medical and nursing expenses had amounted to nearly \$2,000. So that was about \$20,000 to start on. And the jury was instructed that it might allow for that vague something called pain and suffering and for its estimate of the losses which the plaintiff might continue to endure as a result of the accident." The jury, on June 7, 1929, returned a verdict in P's favor for \$50,000, and in July, the defense dismissed its proposed appeal and entered into a compromise settlement for \$40,000.

What was the subsequent medical course of this shattered plaintiff? The rose regained its petals, as can be seen by an extract from a college magazine published in Alabama in February, 1930. "Huntsville friends and music lovers were given a rare treat in January, when E. S. sang for the Art League at the Federation Club House. Music critics have pronounced Miss S's voice richer and better than ever, following the long rest she has had since an accident on an Eastern stage, when a curtain drop fell and seriously injured her. For the summer of 1930 she plans to go to Europe to continue her studies under famous continental teachers. Her charming personality, as well as her lovely voice, makes many friends for her. She is one of the most popular and sought-for singers of the time, and justly so."

This case illustrates several truths about traumatic neurosis: the patient is never as badly off as he appears; the symptoms often lend themselves to dramatic presentation in court; the trier of fact is apt to gain the false impression that the plaintiff has sustained a calamitous permanent disability, and that the injury is entirely ascribable to the defendant's fault. It demonstrates how the stresses, strains and excitement of litigation exacerbate symptoms, causing them on trial to appear more severe than they are. It shows also, how rapid and unexpected may be the complete cure derived from a "green-back plaster" in the form of a compromise settlement. Loss of past and future earnings is always material in fixing compensation, but the same

dramatic triumph may be achieved by a young lady from the 5 and 10 cent store,<sup>15</sup> or by a domestic, provided she has competent directors and producers.

The reader must not assume that we have any animus against traumatic neurosis; we would be the first to proclaim its reality and to dispute those who think that all such cases involve frank malingering. On the other hand, we agree with the court which astutely divined that traumatic neurosis is a condition *sui generis*. So true is this that traumatic neurosis cannot be compensated scientifically on any naive all-or-none theory of causation. Perhaps this warrants our reviewing distorted and distorting notions and factors, to the end of stating certain fundamentals which may help trial lawyer and judge in disposing of such cases.

1. *The plaintiff must be required to establish that he is suffering from traumatic neurosis.* One or two symptoms or findings will not suffice: exaggerated reflexes, for instance, may be found in many situations and do not warrant the diagnosis. Symptoms of pain, headache, dizziness and the like may be due, in whole or in part, to preëxisting illness, not neurotic in character, or to previous major operations, or to hormonal imbalance due to the menopause in a woman between 40 and 50 years of age. In some cases it is possible to show that the plaintiff had a full-blown neurosis before occurrence of the episode asserted to have caused it, in which event juries allow little or no compensation.

The plaintiff must be able to trace the onset of symptoms, with proper time relations, to a focal experience, traumatic or psychic, and to show a clinically accepted progression pattern, important requirements which we shall elaborate later.

There is no doubt that some general practitioners of medicine, or careless witnesses, are prone to fasten the diagnosis of "traumatic neurosis" to a collection of miscellaneous symptoms, many of long standing. Such diagnostic errors lead of course to unjust enrichment of the plaintiff by "sweetening the verdict," and the defendant is thus made to pay for preëxisting poor health which he did not cause. Courts, where new practice and procedure acts authorize the step, should appoint competent, impartial psychiatrists to examine and appraise cases of alleged traumatic neurosis.

2. *Medical examiner and lawyer must determine whether the traumatic neurosis in question represents the more common example of aggravation of preëxisting neurotic impairment or one of the rarer cases of traumatic neurosis arising de novo in a person of average constitution.*

<sup>15</sup> *Kress v. Sharp*, 156 Miss. 693, 126 So. 650 (1930), 68 A.L.R. 167. (P, a clerk in D's department store, was carrying four dozen bath towels in her arms in course of replenishing a counter. The steps she was descending were narrow and poorly lighted. She fell sideways, bruising her hip and back. After resting, she resumed her place at work, but did not continue, at the noon hour going home on the bus and walking part of the way. She had no physical injuries, but went to bed for six weeks, was treated by chiropractors for two years, and at the time of trial, some two years after the accident, was allegedly suffering from *hysteria* with intermixed compulsions and obsessions. Verdict and judgment for P for \$25,000; on appeal, held excessive; judgment reversed and case remanded for new trial on limited issue of damages.)

### A. *The Preëxisting Impairment Cases.*

This task of sorting cases is not so difficult as one might believe. The analysis naturally starts with a full description of the episode and surrounding circumstances alleged to have set off the neurosis. Those extrinsic circumstances which operate independently, and with which the defendant cannot be causally connected, must be excluded. We find that 5/8 or more of the court cases carry their own calling card in that the allegedly causal stimulus is obviously inadequate to affect a person of average nervous and psychic constitution. This fact is usually discernible by a layman, though medical testimony may help. Mind you, we do not say that in 5/8 of cases, there is no *actual causation* of neurotic symptoms, but rather that the average person would not be thus affected, so that appearance of traumatic neurosis is presumptively due to aggravation of previous impairment. In such cases the compensation must be modest, fractional rather than total.

We may demonstrate this group series of cases (the 5/8 group) by a few examples which recur constantly in litigation:

(1) *Common carrier cases:* The train on which plaintiff, a male passenger, was riding ran into the caboose of a freight train. The impact was not great. P, who was then sitting in the smoking car, was thrown forward and struck his head and shoulder lightly against the seat ahead. He sustained no physical injury and continued his business trip for several days, noting advent of mild symptoms referable to his head and neck. Gradually, most diverse symptoms involving every part of his body developed in a rich profusion characteristic of traumatic neurasthenia. P recovered verdict and judgment for \$16,000, and on appeal the award was affirmed.<sup>16</sup>

(2) P, a 44 year old exporter weighing 230 pounds, was sitting at his desk in D's building when an area of plaster 2 feet square fell from the ceiling 10 feet above the floor. It flaked into fine particles as it fell. P either was not struck, and was merely frightened by the noise, or the impact was too slight to inflict physical injury. P testified that he was stunned, and that 15 minutes later he became very nervous. He went to several doctors, but refused to be hospitalized or to undergo lumbar puncture as an aid to diagnosis. The last specialist he consulted saw him 200 times in the course of a year. His pulse rate was accelerated to 90 (normal, c. 70), he had tremors, hyperactive reflexes, was apprehensive, lost weight and showed various symptoms of anxiety neurosis and hysteria. P recovered verdict and judgment<sup>17</sup> for \$3,850, which on appeal was reduced to \$1,000.

In these cases of neurosis following trivial stimuli, a competent psychiatrist usually can find tell-tale confirmation of preëxisting impairment, by close investigation of the plaintiff's past history. However, the inadequacy of the stimulus above should be recognized as sufficient basis for a psychiatric opinion that the particular case is one of idiosyncratic response involving aggravation of a pre-traumatic neurotic trend. It is no answer that plaintiff was previously able to work, as the two facts are not incompatible. Furthermore, ability to work is only one factor entering into the measure of damages in tort actions for personal injury.

<sup>16</sup> St. Louis, I.M. & S.R.R. v. Osborne, 95 Ark. 310, 129 S.W. 537 (1910).

<sup>17</sup> Klein v. Medical Bldg. Realty Co. (La. App.), 147 So. 122 (1933).

B. *Cases where there is no presumption against causal connection between stimulus and neurosis for the reason that the stimulus is of the substantial variety which might cause neurosis in a person of average constitution.*

In this category we place cases of traumatic neurosis incident to severe personal injury, and to psychic stimuli of very harrowing variety. Each case must be closely analyzed, as we cannot draw a generalization that presence of serious injury excludes the possibility that the individual already had a neurotic constitution. The pre-traumatic personality must be studied avidly, in the manner we shall suggest in discussing the Workmen's Compensation cases. Still, this group is sharply demarcated from the group A cases in that here the stimulus is regarded as adequate to produce a neurosis *de novo*. In serious head injury cases, as we have observed, the symptoms may be due to organic injury of the nervous system, to superimposed neurosis, or to both. Less serious injury to the head or to the back, or to other regions of the body, may result in neurosis if medical treatment is conducted in such way as to create fears in the patient that he has suffered serious or irreparable injury.

As we have hinted, though we regard barrel A as containing "bad apples," we do not believe that every apple in barrel B is a sound one. For instance, what more vivid laboratory could we have than war itself? Every soldier on the firing line experiences fear for his life, and may see the most cruel and abhorrent spectacles, psychic stimuli rarely duplicated in civilian life. Yet it is significant that aside from transient nervous shock, which is a *physiological* response,<sup>18</sup> only a small percentage of soldiers develop neurosis, a *psychological* response. There is accumulating evidence that a good portion of these had sub-normal resistance and prior impairment which should have been detected at the induction center by appropriate psychiatric examination. In any event, group B cases give us a residue of traumatic neurosis claims which may prove in the particular case, after adequate study, to merit 100 per cent compensation.

<sup>18</sup> SMITH, H. W., and COBB, S.: Legal liability for psychic stimuli, to be published in *Virginia Law Review* (March, 1944) and in SMITH: *Scientific proof and relations of law and medicine*, 1944, Matthew Bender & Co., Albany, N. Y., vol. I (in press).

Traumatic neurosis developing in soldiers at the front is best known to laymen under the inaccurate term "shell-shock." Readers will appreciate that this term hardly touches the essential cause-effect mechanisms involved. There are many misconceptions about the subject. See, for example, PAINTON, F. C.: There is no such thing as shell shock, *The Readers Digest*, 1943, xliii, 59. The title is catchy but unfortunately the statement it contains is erroneous. It is true that many soldiers exposed to heavy action develop nervous shock, a transient physiological state which may not progress to neurosis if they are kept near the front, treated by sedatives and rest to overcome psychological tensions and fatigue, and are gradually put back into action. The effort here is to prevent the flowering of neurosis by intercepting psychological elaborations. In the last war when such soldiers were invalided to base hospitals and treated as serious injuries with opportunity to brood and meditate, a larger percentage developed neurosis. Treatment near the front enables restoration of many soldiers to useful service who would have been disabled through neurosis under old methods of management. However, it is erroneous to assume that the shift in methodology represents an over-night discovery, for many of the lessons were learned from experience in the preceding World War (1914-1919), and this change in therapy has received attention in psychiatric literature for some years past. See MILLER, E.: *The neuroses in war*, 1940, The Macmillan Co., New York. KARDINER, A.: *The traumatic neuroses of war*, National Research Council, Washington, D. C., 1941.

### 3. *Nervous shock must not be confused with traumatic neurosis.*

As Smith and Cobb state,<sup>19</sup> nervous shock from psychic stimuli produces only relatively transient upset or disability through excessive physiological responses, except where the stimuli have a continuing force or repetitive operation, or where such responses cause injury by acting upon a pre-existing state of vulnerability.<sup>20</sup> Nervous shock per se, no more than trauma, produces traumatic neurosis, for that sequel is not a physiological but a psychological response. The recipient of the trauma or psychic stimulus reacts to it as a *focal experience* or organization point for his neurotic symptoms. Courts err when they fail to perceive this distinction and treat nervous shock and traumatic neurosis as the same phenomenon. Many persons will suffer transient nervous shock from psychic stimuli such as great fear, who will never progress to the development of a traumatic neurosis. Conversely, some persons who sustain no immediate nervous shock will begin to develop neurosis a few hours or a few days after the *focal experience*, thus illustrating that independent forces and more devious mechanisms are involved in the appearance of neurosis.

*Example:* P, a maid in the house of X, was engaged to N, an interned German (first world war). D, a private detective, desired to examine letters in X's house to determine whether or not they were forged, as he suspected. He said he was from Scotland Yard, representing the military authorities, and that he was looking for a woman who had been corresponding with a German spy. He hoped by this threat to induce P to give him access to the letters. P was frightened, went to the police at 9:00 p.m., and cried five minutes before she could tell her story; then sat on the stairs of her residence from midnight until 5:00 a.m. with a police whistle in her hand, without sleeping. She claimed that this experience caused her to develop neurasthenia. The evidence showed that previously P had been in a state of psychological turmoil from continued protests of relatives against her maintaining contacts with the German, N. P's physicians admitted on cross-examination that her neurotic symptoms might as likely be due to anxiety about N as to the episode mentioned. This would have rendered proof of causation of the neurosis ambiguous, had the court not held that P's account of her nervous shock corroborated the theory that her neurosis was the result of her fright. P recovered verdict and judgment for 250 pounds and this was affirmed.<sup>21</sup>

On the principles we have mentioned, we would say that P's immediate responses were compatible either with fright and transient nervous shock or preëxisting neurosis, whereas proof that the episode actually produced P's neurasthenia was conjectural.

### 4. *In the usual case of traumatic neurosis, symptoms are multiplied and exaggerated as a result of independent causes, and the patient's plight appears to be worse than it is.*

<sup>19</sup> SMITH, H. W., and COBB, S., *op. cit. supra* f.n. 52.

<sup>20</sup> For instance in more than 25 per cent of the litigated cases of alleged injury due to fright, the described harm was miscarriage of a pregnant woman. The authors mention such conditions as angina pectoris, a heart disease in which injurious or fatal attacks may be precipitated by excessive emotional stimuli. They also list diseases for which there is clinical evidence that psychic stimuli may precipitate or aggravate an attack.

<sup>21</sup> Janvier v. Sweeney (Eng.), 2 K.B. (1919) 316, 9 B.R.C. 579, 88 L.J.K.B. N.S. 1231, 63 Sol. Jo. 430.



Persons in group A (trivial stimulus cases) are almost always very suggestible. They can be led to believe that they must have struck their bodies on the cross bar of a street car seat when no such bar or obstruction was there. Their symptoms are greatly aggravated by the anxiety and excitement of litigation, a fact which the defendant is entitled to prove. These apprehensions about the oncoming trial are due partially to fears that their claim of injury will be disbelieved or held in contempt for want of objective lesions. Also, the self-serving mechanisms involved in neurosis invariably cause some degree of unconscious exaggeration or malingering in respect to symptoms, as the neurotic desires to be believed and wants his complaints to be convincing. Suggestions made by relatives and lawyers and the continuance of disability payments are additional extrinsic factors which cause neurotic symptoms to be aggravated or exaggerated. Thus the neurosis is not so bad as it seems, and the conclusion of litigation will usually cause many of the symptoms engendered by it to disappear. In our opinion 20 per cent to 60 per cent of the disability can be safely assigned to these extrinsic factors and expected to vanish upon settlement of the case.

5. *One must bear in mind that 12 to 36 months between stimulus and trial is a not unusual time interval, due to congestion of the courts, and that part of the neurotic symptoms may be traceable to independent, post-accident causes.*<sup>22</sup>

6. *To prove that the stimulus (traumatic or psychic) created by defendant actually caused neurotic symptoms, it must be shown that some or all of the characteristic symptoms appeared within a reasonable time after receipt of the stimulus.*

A vulnerable person may begin brooding a long while after an accident regarding what might have happened to him and in that event to his family, with the result that a late anxiety neurosis develops which should not be compensable. Causation is obscure enough, at the best, in traumatic neurosis cases, and proof of causal connection becomes too conjectural to be trusted, when a symptom-free period of more than a few hours, or at most of a few days, separates stimulus and onset of the neurosis. The plaintiff must be required to prove satisfactory bridging symptoms to connect stimulus and late neurosis, such as speedy and persistent complaints of pain, substantial nervous shock, or prompt and continuing symptoms showing altered psychological behavior.

<sup>22</sup> The facts of *Hunter v. Fleming* (Mo. App.), 7 S.W.(2d) 749 (1938), illustrate this possibility. On June 29, 1925, P, a married woman, was with her husband in the family car when it stopped dead on a street car track. D's conductor could see the stalled automobile 200 feet away but he continued to approach at a speed of 12 to 15 m.p.h. P screamed and waved her arms, but a slight collision occurred. This modest impact caused P to sustain superficial head injuries and a few bruises but no objective injuries of any consequence. Thereafter P developed nervous symptoms consistent with *neurasthenia* but proof of cause-effect relationships revealed that on Jan. 28, 1927, P had suffered a miscarriage. The examining physician attributed to this latter cause part of the symptoms of which P complained at the time of trial.

Thus defendant's counsel must make close inquiry into plaintiff's post-accident medical history to see if other illnesses or accidents have occurred which might account for some or all of P's symptoms or disability.

7. *Traumatic neurosis cannot be regarded as a permanent disability.*

Many courts have upheld excessive awards for traumatic neurosis because of their mistaken impression that the condition involves permanent disability. This is perhaps the most common misconception which now distorts the calculation of a just compensation. Many medical witnesses contribute to this misapprehension by testifying loosely that the condition "is of uncertain or indefinite duration."<sup>23</sup> We do not have adequate medical grounds to warrant such a prognosis. There is extremely good evidence that the average case of traumatic neurosis recovers within three to five years or even less, following the time a lump sum settlement is effected or the litigation is terminated.<sup>24</sup> There may be rare exceptions of a certain amount of irreversible injury due to the atrophy of disuse, if a hysterical contracture persists long enough for these secondary dangers to occur.

Some courts, in deciding that the traumatic neurosis is probably a permanent rather than a temporary disability, make capital of the fact that the neurosis has continued for a year or two between injury and date of trial, and without improvement. The inference is attractive, but hardly trustworthy, as pendency of a claim for compensation operates in a potent way to keep the neurosis in full bloom.

Testimony that traumatic neurosis may lead to brain abscess shows crass ignorance or deliberate imposition on the part of a medical witness, for brain abscess is due to infection, and the risk of this is not increased unless it be shown that the traumatic wound caused infection which then reached the brain. Even in appropriate cases, such a complication would occur or not within days or weeks of the injury. Another claim sometimes made by medical witnesses is that the neurosis may pass into psychosis, that is to say, frank insanity. Some courts seem to think that neuroses and psychoses are brothers and sisters. Such a relationship is not proved, nor indeed credited: we have no scientific proof that neurosis is a step on the way to psychosis.<sup>25</sup>

<sup>23</sup> This practice is a widespread and pernicious habit among expert witnesses; it lays a false foundation for a judicial inference that the disorder is a permanent disability.

<sup>24</sup> If anything, this allowance errs on the side of liberality. It is intended as an outside limit, for most cases recover more speedily.

<sup>25</sup> Judicial skepticism has kept some courts on the right path in this matter. In *Louisville & N.R. Co. v. Creighton*, 106 Ky. 42, 50 S.W. 227 (1899), P, a 38 year old woman, had received injuries in trying unsuccessfully to rescue a three year old child from the path of an oncoming train. Later she developed hysteria, and on the trial her physician predicted that this might progress to insanity. The jury awarded her a verdict of \$17,500, but on appeal a judgment for this amount was reversed as excessive, the court pointing out that P seemed to be in possession of all her faculties and "she testifies . . . very lucidly in this case."

In *Friedman v. United Rys. Co. of St. Louis*, 293 Mo. 235; 238 S.W. 1074 (1922), P was motoring with her husband when their automobile was involved in a collision with D's street car. P was rendered hysterical but not unconscious by the impact, and en route to hospital in the car of witness Woody, P exclaimed to her husband, H: "Oh, daddy, you have killed me," to which H replied: "It was your fault, sweetheart, you grabbed the wheel." Thereupon, P replied: "I know it was, I don't blame you, sweetheart." This testimony was objected to on trial on the ground that P's hysteria rendered her mentally incompetent, but the trial court admitted the evidence as an admission against interest and the jury returned a verdict in D's favor. Held, on appeal: affirmed.

Courts are concerned about the possibility that an injured person may be imposed upon in the making of a compromise settlement. One who claims he was fraudulently imposed

8. *Technics of courts in dealing with allegedly excessive awards for traumatic neurosis.*

If a verdict is excessive, the trial court may require the plaintiff to remit a specified amount of the award, on pain of granting the defendant's motion for a new trial. If an appeal court desires, it can require a still further remittitur on pain of reversing the judgment and remanding the cause for a new trial. A conventional test of excessiveness is whether the verdict is so large, in going beyond fair compensation, as to shock the court's conscience and to require an inference that the jury was motivated by passion and prejudice.<sup>26</sup>

In practice, the courts act upon a variety of considerations as proper grounds for holding large awards excessive:

(1) Neurotic symptoms may be caused or aggravated by environmental influences or the circumstances of litigation, but the defendant is not liable for a worsening of plaintiff's condition produced by such independent causes.

(2) A judgment in plaintiff's favor may be reversed because the verdict rests on the jury's unwarranted assumption that traumatic neurosis is a permanent disability.

(3) Judgment may be reversed because the verdict is obviously excessive, but expert evidence adduced on the trial is not adequate to enable the appeal court to say how much the award should be reduced by remittitur.

(4) A verdict may be excessive because of the jury's failure to give proper weight to evidence that plaintiff's symptoms were in part due to pre-existing impairment of his nervous system or bodily health.

(5) A verdict may be considered excessive because of strong evidence pointing to conscious malingering.

(6) A verdict insupportable on the evidence calls for reversal of judgment, as, for instance, where the stimulus was patently inadequate to cause neurosis in an average person, and testimony indicated that P was already subject to that complaint.

Comparative competency of opposing experts may be of controlling importance in deciding inadequacy. Thus, a verdict which rests on testimony of general practitioners, not founded on a reasonably systematic examination of the nervous system, may require to be reduced or set aside where op-

upon is permitted by some courts to show his depressed state of health at the time, as one circumstance, even though it does not establish mental incompetency. Thus it has been held that a personal injury plaintiff who seeks to set aside a release on the ground of fraudulent procurement, is entitled to show that she was a profound neurasthenic at the time it was executed. *Wilson v. San Francisco-Oakland Terminal Rys.*, 48 Cal. App. 343, 191 Pac. 975 (1920). As neurosis does not impair the intellect, such evidence should not be regarded as a ground for cancellation of the release, but merely as a circumstance directing closer scrutiny of the alleged fraud or imposition.

Early stages of schizophrenia, one type of psychosis, may produce symptoms similar to neurosis, causing an error in diagnosis, but any such confusion will be resolved as the psychosis progresses, and there is no evidence that neurosis progresses into schizophrenia.

<sup>26</sup> *Carton v. Eyres & S. Drayage Co.*, 117 Wash. 536, 201 Pac. 737 (1921).

posite opinion evidence is given by defendant's experts, skilled neurologists, based upon exhaustive neurological examinations.

(7) If a plaintiff unreasonably neglects to minimize his own damages, this is adequate ground to refuse him full compensation for aggravation or prolongation of his injury.

If the prospective defendant tenders medical care which would have cured or ameliorated plaintiff's disability, and the latter rejects it, the principle mentioned applies. However, sending a case of traumatic neurosis into an ordinary hospital frequently makes symptoms worse. To make certain that his tender of treatment is adequate, the defendant should offer care in a quiet and proper place by a qualified neuropsychiatrist.

(8) Instances exist where appeal courts have reduced verdicts on the ground that plaintiff's lawyer made improper argument to the jury. As it is difficult to say how much the inflammatory remarks swelled the verdict, it is usually more satisfactory to deal with this prejudicial error by reversing the judgment and ordering a new trial.

Our opinion is that all cases of traumatic neurosis, and particularly those following trivial stimuli, should be compensated on a conservative basis with damages restricted to modest levels. This point of view seems to us to be required by several considerations, namely:

- a. The basis of compensation depends upon subjective symptoms;
- b. There are independent causes, of substantial weight, operative in all traumatic neurosis cases;
- c. The defendant's act is usually a trivial stimulus which merely calls forth expression of a preëxisting neurotic diathesis or constitution, and thus tends to be a trigger mechanism rather than a substantial cause;
- d. Diagnosis and evaluation depend on statements of the patient as to nature and severity of his symptoms, and there may be no adequate verification or method of objective measurement;
- e. Malingering is very difficult to prove, but is often present, and almost always there is unconscious exaggeration of symptoms.

#### B. *Traumatic Neurosis in the Field of Insurance Law.*

*Workmen's Compensation Insurance:* The duty to insure the employed workman is statutory and the idiosyncratic person is not excluded.<sup>27</sup> He is

<sup>27</sup> *Crowley's Case*, 223 Mass. 288, 111 N.E. 786 (1916), allowed full compensation for disability due to aggravation by accidental injury of preëxisting dormant syphilis. Braley J. spoke the majority view as well as the rule for Massachusetts when he said in his opinion:

"The statute prescribes no standard of fitness to which the employee must conform, and compensation is not based on any implied warranty of perfect health or of immunity from latent and unknown tendencies to disease which may develop into positive ailments if incited to activity through any cause originating in the performance of the work for which he is hired. What the legislature might have said is one thing; what it has said is quite another thing; and in the application of the statute the cause of partial or total incapacity may spring from and be attributable to the injury just as much where undeveloped and dangerous physical conditions are set in motion producing such result, as where it follows directly from dislocations or dismemberments or from internal organic changes capable of being exactly located."

brought within the policy by being put to work, and is entitled to *some* compensation if his injury resulted from an accident sustained in the course and scope of employment.<sup>27</sup> Observe that we do not specify *how much* the claimant should recover, for this must be determined by deciding what part of the total injury is attributable to the accident.

*War Risk Insurance:* Here the government, as insurer, comes under a *duty* to pay benefits to the insured person in certain contingencies. There is no dereliction or breach of duty unless the insurer refuses to pay when a stipulated contingency has occurred, namely, proof by the veteran that he incurred a service-connected total and permanent disability before the date his policy lapsed for non-payment of premiums.<sup>28</sup>

*Life, Health and Accident Insurance:* The insurer, by contract, comes under a *duty* to pay benefits to the insured person if certain contingencies occur, such as disability or death, and these are not brought about by one of the excepted causes. Many such policies provide that they are void for breach of warranty if the insured takes out the policy without disclosing presence of a material disease. Accident policies often endeavor by their language to exclude liability for injury due in whole or in part to preëxisting disease. In practice these clauses are construed favorably to the insured.<sup>29</sup>

The reader will appreciate the fact that transactions which give rise to tort actions usually involve strangers, or the actor has not had occasion to examine the person acted upon. Very often the actor derives no benefit from presence of the person acted upon, and duty must depend upon risk of injury. That reasonable enterprise may not be discouraged, we argued that the law should hold an actor owes no special duty of care to the idiosyncratic person unless he knows or should know of the latter's excessive vulnerability.

Relations of insured and insurer do not involve two strangers. There

<sup>28</sup> It is not enough for P to prove that he was *permanently disabled* at the time the policy lapsed; he must also prove that he was then *totally disabled*. P does not establish his right to benefits if a partial disability at date of lapse did not become total until some subsequent time. (Attention is drawn to the fact that war risk policies are no longer being issued; in the present war the National Life Insurance available to service men insures against the risk of death only.)

<sup>29</sup> If a policy provides for payment of benefits in event insured becomes disabled, this includes functional as well as organic disease and thus *traumatic neurosis* or *hysteria*. *Butler v. Prudential Ins. Co. of America*, 117 Pa. Super. Ct. 367, 177 Atl. 335 (1935). But in view of the fact that *traumatic neurosis* is not entitled to be rated as a total and permanent disability, it is not clear how a claimant can ever establish his right to recover benefits under a clause (as in the *Butler* case) which requires such proof. In the *Butler* case there was some evidence that the neurotic symptoms were due to actual brain injury, and such a case may involve permanent injury.

If the disability clause requires not only "incapacity to transact any and every kind of business" but entire and continuous confinement to bed under a physician's care, a *neurasthenic* who cannot attend to business but is able to travel for his health, is not entitled to benefits. *Bradshaw v. American Benevolent Ass'n*, 112 Mo. App. 435, 87 S.W. 46 (1905).

Continuous progression of *traumatic neurosis* symptoms for almost two years after injury to eye, producing delayed disability, will not defeat right to benefits. *Thompson v. Aetna Life Ins. Co. of Hartford*, 177 S.C. 120, 180 S.E. 880 (1935).

Whether treatment for *neurosis* within two years prior to date of policy was treatment of a "serious disease, injury, or physical or mental condition" which would avoid policy was a jury issue in view of medical testimony. *Potter v. Metropolitan Life Ins. Co.* (Superior Ct. Pa.), 27 Atl. (2d) 703 (1942).

is a continuing relationship, ushered in by a contractual assumption of risk. Furthermore, the employer, the government, the insurance company not only can but do subject the inductee to rigid physical examination. They know or should know if the inductee is idiosyncratic. For all these reasons the duty assumed includes these frail fellows. We clinch our argument here by asserting that in the great majority of cases the inadequate personality can be detected by proper neuropsychiatric examination. The incipient or early neurotic can be spotted.<sup>30</sup>

*Traumatic Neurosis in Workmen's Compensation Cases.*

The Workmen's Compensation Law introduces a somewhat different philosophy regarding right to compensation for injury. We cannot ignore this fact in projecting a rationale for compensation of the traumatic neuroses.

At common law, the employee who sought to hold his master in damages for personal injury received in course of his work was required to prove some negligence or fault on the part of the employer. He was barred by his own contributory negligence or if it appeared that his injury was caused by the negligence of a fellow employee. He assumed the risk of injury from apparent hazards arising from working conditions or from the state of his master's premises. This is still true of an employer of one employee or of a number less than the statute provides for; moreover, the employee may elect his common law rights when he is employed.

Workmen's compensation laws have wrought an innovation: under them benefits are payable to an insured workman if he is disabled by an accidental

<sup>30</sup> The detection of such persons to the end of excluding them from the armed services has been a noteworthy social contribution of medical examiners.

*Data re 21-36 year old registrants:* Of two million registrants, it was estimated by the writers on the basis of 19,923 actual examinations by local boards and by Army induction stations, and on the basis of summary reports from local boards, that about 50 per cent were established to be unqualified for general military service, 900,000 for lack of physical and mental qualifications and 100,000 for lack of educational qualifications. Of these 900,000, Selective Service, on the ground of mental and nervous defects, rated 8,000 registrants as qualified only for limited military service and 30,000 disqualified for any military service. The Army, on the same ground, rated 19,000 as unqualified for general military service, thus yielding a total of 57,000 registrants (or 6.3 per cent of the 900,000 unqualified persons) rejected for mental and nervous defects. Of every thousand men examined, 18.2 showed mental disorders and 22.8 showed nervous disorders, a total of 41 per thousand.

ROWNTREE, L. G., MCGILL, K. H., and FOLK, O. H.: Health of selective service registrants, Jr. Am. Med. Assoc., 1942, cxviii, 1223.

*Data re 18 and 19 year old registrants:* This study, based on a sample of 45,585 reports of physical examination and induction, covering December 1942, and January and February 1943, showed that of white youths called up for physical examination, 23.8 per cent were rejected either at local boards or at induction stations, whereas the rejection rate for negro youths was 45.5 per cent. Of every thousand men examined, 27.6 were rejected for mental disorders and 14.8 for nervous disorders, or a total of 42.4 per thousand. Of these 42.4, 15.2 per thousand were rejected for psychoneurotic disorders.

The authors hasten to explain that while the rejection rate for the younger age group is about the same as for the older registrants, some caution should be exercised in drawing conclusions from this for the reason that "a large proportion of physically fit youths were not liable for examination either (a) because of previous enlistment in the armed forces, (b) because of programs that postponed examination and induction until a course of training had been completed or (c) because of employment in war industry or agriculture."

ROWNTREE, L. G., MCGILL, K. H., and EDWARDS, T. I.: Causes of rejection and the incidence of defects among 18 and 19 year old Selective Service registrants, Jr. Am. Med. Assoc., 1943, cxxiii, 181.

injury arising out of and in the course and scope of employment. The injury is measured by comparing disability to work after the accident with disability before it. If a workman afflicted with preëxisting heart disease is able to get to his job and perform it, but as the result of an accidental injury which would do little or no harm to the average person becomes disabled, this whole disability is imputed to the accident and so compensated. In contrast with tort law, personal injury is not compensable, unless scheduled, or unless it produces some disability to work as before. This difference in the basis for calculating the measure of damages in workmen's compensation cases and in tort law is a significant one. In tort law it is material that the vase was cracked before the accident occurred; in compensation law it is of no moment that the vase was cracked before the accident if it would still hold water. Thus prior impairment or idiosyncrasy of the workman is immaterial in compensation law, if the *whole* disability to work is due to aggravation of preëxisting poor health by accidental injury.<sup>31</sup> Even so, workmen's compensation insurance is not social insurance. Should society some day provide for automatic compensation of its disabled members, preëxisting idiosyncrasy or vulnerability will no longer be of consequence. The only issue will be: Is there a genuine disability or is the citizen a lazy loafer who is malingering? We have not yet attained to that Utopia and in the meantime it is important to recognize that the concept of *fault* in altered form is still used as a device for making the particular employer bear risk of injury by paying premiums. The *fault* is not common law negligence, but involves a new principle of responsibility and a partial step toward social insurance—incriminating the business on the score of risks produced in its conduct; *ergo*, the injury is not compensable unless it is an injury arising out of and in the course and scope of employment. From this it follows that if disability is made up of two parts, one due to accidental injury, the other arising independently of it, the claimant is entitled to compensation only in respect to the former. If a weakened or diseased heart is injured by an accidental strain, the resulting disability follows directly, and usually without suspicion of new and independent causes. Not so in the case of the neurotic personality: part of the resulting disability is due to the effect of the accident on the set stage, but new and independent factors always operate to exaggerate the disability. The defect is one in actual causation, and justice can be done only by restricting benefits to that part of the disability due to the accident. Some of the compensation commissions have perceived this logical barrier to full compensation of traumatic neurosis. If they find a claimant is totally disabled from neurosis, but believe the accident is responsible for only 20 per cent of the symptoms, they enter an award for a 20 per cent total disability. This device, one should note, may involve partitioning of causation, a scientific procedure foreign to the common law, which follows an

<sup>31</sup> The most spectacular instance is the practice, in a majority of jurisdictions, of allowing full awards for disability due to aggravation of preëxisting heart disease by accidental injury arising out of and in the course of employment.

"all or none" theory of causation. At common law, a defendant's conduct is either a substantial cause (sole or concurring) of the plaintiff's injury, or is not the cause at all. Apportionment of disability from neurosis between accident and independent causes is desirable to the fullest extent that the law of the jurisdiction permits. In jurisdictions where complete apportionment might be sanctioned, the medical examiner should endeavor to partition causation, and thus disability, between the accident and independent factors, as follows:

1. Percentage of disability from traumatic neurosis attributable to the accident (10 per cent to 50 per cent); the stimulus involved in the accident will be found to range from a mere trigger mechanism to a substantial cause apt to produce some nervous shock or symptoms in an average person.

2. Percentage of disability from traumatic neurosis attributable to pre-traumatic neurotic constitution or to non-compensable independent causes. (Deduct percentage determined above from 100 and verify by thorough study of pre-traumatic neurotic constitution, and of the post-accident factors likely to be aggravating or exaggerating symptoms.)

Obviously no exact mathematical formulae can be applied, for the apportionment between accident, pre-traumatic neurotic constitution, and post-accident causes requires sound clinical judgment of an impartial, competent neuropsychiatrist.

The pre-traumatic personality is investigated by appropriate inquiries directed toward determining what neurotic tendencies or symptoms were already present before the alleged injury occurred. These include:

1. Medical history: What doctors has patient seen and for what complaints? The medical history of a neurotic shows vague symptoms, often-times multiple, which do not incriminate any particular organ.

2. Past school record.

3. Matrimonial harmony or discord.

4. Attitude toward job. Nature of past employment. Work record and promotions. Ability to hold strenuous job. Neurotics tend to remain for long periods at jobs where special concessions of various kinds are made to them.

Some compensation acts would seem to authorize commissioners to exclude compensation both for preëxisting disease or neurotic diathesis and for disabling symptoms arising from subsequent and independent causes. What can be done should be done in both directions. It is likely that the present practice of granting full compensation for the aggravation of preëxisting disease by accidental injury is logically erroneous and socially unwise in that it tends to exclude those with disabilities from employment. It is true one can plausibly argue that as the employer, by medical examinations, has a sieve for sifting, he must assume the full risk of total disabilities partially due to accident and partially due to preëxisting disease or extra vulnerability.



Let us see how this doctrine works out in point of social effect. The average incipient neurotic is capable of holding a job and supporting himself. The employer knows, however, that a "tiny touch" may cause the incipient neurotic to develop a compensable total and permanent disability. Under the "full liability" theory subnormal or handicapped people will be weeded out, and excluded from industry. This is not theory but fact, well illustrated by the almost complete exclusion of epileptics from industry. If the doctrine for which we contend be followed, a medical auditor, referee or impartial examiner would carefully study the case and apportion the disability between accident and preëxisting causes. The insurer, and indirectly the employer, would not pay 100 per cent on a traumatic neurosis case, but only 10, 20, or 30 per cent, or what was fair in light of all facts. This policy would be eminently fairer to the employer and it would tend to make the impaired person employable on a just basis. We favor legislative changes in compensation laws designed to permit scientific apportionment of causation in all cases. The alternative is to see the practice grow of sagacious employers using medical examination to screen out of useful service those whose health may be slightly impaired but who are yet capable of a productive rôle in the industrial machine. The third alternative is a statutory provision authorizing the impaired employee to sign a disability "waiver" in going to work.<sup>32</sup> Such a waiver releases claims for benefits in respect to accidental injury sustained only because of a specified preëxisting defect. Statutory waivers help to make handicapped persons employable, but partitioning causation is a more scientific and equitable method of attaining the same objective, for it permits partial compensation.

Most workmen who develop traumatic neurosis can be got back to work. The process requires sympathy and patience on the part of employer and proper psychiatric care. After allowing compensation for traumatic neurosis as a matter of course, the judge may be surprised to find months or years later that the workman's condition is no better. At this point the court will feel constrained to cut off further compensation, and often this is done on the ground that the claimant has stayed away from work an unreasonable time or is malingering. This is a convenient fiction or reflects ignorance of the

<sup>32</sup> The Massachusetts Workman's Compensation Act, sec. 46, provides:

"No agreement by any employe to waive his rights to compensation shall be valid, but an employe who is for any reason peculiarly susceptible to injury or who is peculiarly likely to become permanently or totally incapacitated by an injury may, at the discretion of the department and with its written approval within one month of the beginning of his employment, waive his rights to compensation under sections 34, 35, and 36, or any of them."

This provision is expected to make many partially disabled war veterans employable. The Supreme Judicial Court of Massachusetts has not yet had occasion to define the phrases "peculiarly susceptible" and "who is peculiarly likely." However, Mrs. Emma S. Tousant, chairman of the Massachusetts Industrial Accident board, explains the waiver provision thus: Assume: . . . "a veteran had a bullet hole in his wrist. A bone had been removed from it, leaving his wrist weak. Now, if he sustained an injury at work which stemmed out of that wrist weakness, he could *not* get compensation. But if an elevator dropped and he broke a leg, he certainly would collect, just as any other workman in that elevator would collect, because that injury had nothing to do with the weak wrist." Boston Traveler, Tuesday, Oct. 5, 1943.

basic situation. Remember that benefits paid to a disabled workman are not so large as the earnings he is losing. He does not profit financially by continuance of his neurosis. He has initial symptoms which produce some disability. If he tries to return to work, a foreman not imbued with the ideal of gradual and sympathetic rehabilitation, may deepen the neurosis by putting him to work at once on his old job. The demands are too great, and the workman's failure aggravates his neurosis. During this time, the insurer's agents are apt to be investigating and questioning the reality of the claimant's illness. The claimant's financial obligations remain fixed while his income is cut in half. He may acquire feelings that he is the victim of social injustice. These factors cause the gorge of the workman to rise, producing psychological tensions which increase the neurosis still further. Some of our large industrial companies have practically no traumatic neurosis among their employees because they follow a program of sympathetic rehabilitation. The sick man is continued at his regular salary; the reality of his complaint is not put in issue unless frank malingering is involved, and the employee is given the best medical care. He is returned to his job at an early date under sympathetic oversight and by easy stages calculated to rebuild his lost confidence. It will be observed that everything possible is done to dissipate the sense of insecurity and frustration. The same rationale of rehabilitation will be required to restore veterans with war neuroses. Both in the compensation cases and in the veteran cases, a single lump sum payment is preferable to protracted payment of benefits. This should be coupled with provision for giving the neurotic a sense of security and a program of gradual rehabilitation, until his restoration is accomplished.

It is a common mistake in compensation proceedings, as in the tort cases, to regard traumatic neurosis as a permanent disability. It is not a provident thing to keep reopening awards and perpetuating installment payments, as some commissions do. Traumatic neurosis cases should be disposed of once and for all, by one award and not piecemeal.

*Alleged Conversion of "Traumatic Neurosis" to "Compensation Neurosis."*

*Example:* C developed a traumatic neurosis from an accident received in course of employment. This expressed itself as hysterical paralysis with certain side symptoms. C was hospitalized and under psychotherapy lost practically all his symptoms, so reporting to I, the commission's impartial medical examiner who had first diagnosed hysterical paralysis. In a few days the hysterical symptoms returned. I testified before the commission on application for further benefits, that C had been cured of hysterical paralysis due to traumatic neurosis and that return of symptoms was due to compensation neurosis. C's claim was denied on the ground that the disability from which he now suffered was not caused by the accident.

We do not recognize "compensation neurosis" as a condition apart from the original "traumatic neurosis," for the former is only one part of the total neurotic reaction to the original injury. The idea of a conversion in mid-stream from compensable to non-compensable neurosis is a tempting device

to enable curtailment of benefits in select cases, but it is not medically sound. Furthermore, we would stress the fact that temporary remission of symptoms in traumatic neurosis under special psychotherapy is no proof of cure. In such cases the neurotic symptoms are notoriously apt to recur.

On the other hand, as we have pointed out heretofore, a vulnerable person may begin brooding a long while after the accident about what might have happened to him and to those financially dependent upon him, thereby developing a late anxiety neurosis which should not be compensable. As pointed out in discussing the tort cases, proof of causal connection becomes more conjectural as the symptom-free time interval between alleged stimulus and effect lengthens. It may be denied if satisfactory "bridging symptoms" do not appear at once, or within a few hours or days, such symptoms being speedy and persistent complaints of pain, substantial nervous shock, or prompt and continuing deviations in psychologic behavior. The later a neurosis is in attaining "full bloom," the more reason there is to suspect that independent and non-compensable factors may be operative.

*Traumatic Neurosis in War Risk Insurance Cases.*

The government is employer of the soldier and the latter is truly a servant of the state, drawing modest compensation for the heavy risks to which he is exposed. We draw much nearer to the concept of social insurance when we encounter the war risk insurance policy. Courts should and do follow the principle of liberal construction in dealing with the legal claims presented by the veteran.

Thus, it is held that if the disability is a mental or functional condition, late diagnosis some months or years after lapse of the policy is not necessarily incompatible with the veteran's contention that he was totally and permanently disabled from a service-connected cause when the policy lapsed. This is put on the ground that such conditions are more difficult to discover and diagnose than physical injuries or organic diseases. It is further held that a rather long work record between lapse of policy and filing of claim does not disprove the veteran's total and permanent disability during the interim period, particularly if the evidence shows much shifting of jobs and unsuccessful efforts at adaptation to steady employment. He is not confined to evidence of his physical condition at time the policy lapsed, though this is the real issue, but is permitted to show the subsequent unfoldment of his disability in proving that he was totally and permanently disabled when the policy lapsed. These concessions are more safely made in respect to the psychoses than in regard to the neuroses.

War risk insurance issued during the first world war paid benefits for total and permanent disability incurred before the policy lapsed. Veterans who let their policies lapse upon leaving service, or shortly afterwards, have continued to file suits claiming a present disability had become total and permanent before the policy lapsed. In testing the alleged cause-effect relationship in a neurosis case, we cannot accept the hypothesis of a service-

connected causation where there has been a substantially symptom-free period of as much as four to six months after lapse of the policy before appearance of the characteristic symptom-complex.

*C. Recurrent Problems of Trial Practice.*

Rules of pleading in legal proceedings are intended to give each party notice of contentions his adversary will seek to prove at time of trial, thus eliminating surprise and affording him fair opportunity to organize counter-testimony. The pleader is required to set forth the ultimate facts upon which he rests his cause of action or defense, but not to plead his detailed evidence. In personal injury litigation, it is generally enough for a plaintiff to plead the medical diagnosis of the condition allegedly caused by a defendant's dereliction, this entitling him to prove, without pleading, all the symptoms characteristic of that medical complaint. This rule has been held applicable to traumatic neurosis. There is some question about the wisdom of so holding, for we have seen that traumatic neuroses are not ultimate entities of fixed connotation, but symptom-complexes. The symptoms form the basis of compensation, and they vary widely in their nature. For that reason a defendant is not given fair notice and opportunity to organize counter-evidence effectually unless the plaintiff be required to plead the type of the neurosis and its leading symptoms.

In some instances defendants have requested the trial court to charge the jury that traumatic neuroses, because of their subjective nature, require more positive proof or more conservative compensation. The usual response is for the court to decline, on the ground that such a charge would unfairly prejudice the plaintiff's case. The assumption underlying the requested charge is correct, for the several reasons we have discussed. The desired effect may be obtained by charges which stress more fully than heretofore the requirements of causation, and the duty to exclude from compensation symptoms produced or aggravated by extrinsic causes. Trial courts should also prevent, as far as possible, undue dramatization in the trial of traumatic neurosis claims. Such presentations tend to produce excessive verdicts, yet rules of court can hardly succeed in curtailing the dramatic possibilities entailed in trial before a jury. This being true, the need is all the greater for trial and appellate courts to scan awards with watchful eye and to apply freely the secondary corrective of reducing excessive verdicts.<sup>33</sup>

<sup>33</sup> Little can be done, for instance, under rules of court to curb melodramatic exhibitionism.

In *Kress v. Sharp*, 156 Miss. 693, 126 So. 650 (1930), a case of traumatic hysteria, plaintiff's attorneys put on a royal circus. One act was to have P examined in a room of the court house during progress of the trial, with several young ladies (X, Y and Z) present. P's condition was aggravated by this procedure and she went into hysterical exhibitions. X, Y, and Z were immediately put on the witness stand and conveyed their impressions to the jury, testifying, in effect, that P was a physical and mental wreck. The jury returned a verdict in P's favor for \$25,000. The Mississippi Supreme Court took P's attorneys and physicians to task in a trenchant opinion. It held the verdict was grossly excessive and reversed the judgment for new trial on the limited issue of damages.

*Malingering.*

A recurrent problem is how to prove suspected conscious malingering. This issue may arise in any litigated case of neurosis, directly or inferentially.<sup>34</sup> Malingering cannot be predicated on momentary disappearance of a hysterical contracture when the patient's thoughts are diverted, as this is a normal phenomenon. Difficulty in proving malingering is increased by the fact that no two symptoms, however diverse, are incompatible in traumatic neurosis, for aches and pains from head to toe with multiple side symptoms, none pointing to a specific disease, are diagnostic evidence of psychoneurosis.

How, then, is one to test malingering?

1. A careful study of the pre-traumatic personality and history is valuable. If the person was an incipient neurotic one will find that he has been going to doctors with vague and diffuse complaints, that he has had difficulty in personal adjustments or relations, or that he works where the employer will make special concessions to his state of health. If this type of person is revealed, his neurosis is most likely real and any intentional malingering will be by way of exaggerating severity of his symptoms. The careful medical examiner can usually judge the extent of "staged" exaggeration.

2. If the person has no such past history, he may be a frank malingerer and one must focus sharply on adequacy of the described stimulus to produce traumatic neurosis in a person of average constitution.

3. Conscious malingering in respect to hysterical blindness or some other ailments, can be tested by trick mirrors or lenses and other apparatus designed to make the person believe one member of his body is being tested when in fact another is being examined.

4. Hysterical contracture, if it has not continued so long as to produce actual physical impairment, will disappear completely under anesthesia, and in this way can be distinguished from an organic lesion. This test demonstrates whether the contracture is organic or psychological in origin but proof that it is of the latter variety does not prove conscious malingering.

5. All sorts of methods must be used to prove that the subject actually performs the functions which he asserts have been lost. Claim agents may take motion picture "action shots," persons who call may find the hopeless cripple walking, or the like, and other evidence contradictory of the plaintiff's claims may be discovered. Where a plaintiff confesses in court that she purposely exaggerated the severity of her symptoms, this circumstance will require closest scrutiny of the amount of damages awarded by the jury, but will not upset it, if without reliance on plaintiff's testimony, one can see from independent medical evidence that the plaintiff did suffer substantial injury for which the award is not excessive.

<sup>34</sup> *Conscious malingering*: We adopt Wechsler's definition that "the individual becomes a malingerer only when he consciously and purposely, in order to deceive, to evade responsibility, or to derive gain, feigns illness and voluntarily tries to reproduce signs and symptoms which he really does not have, or extravagantly exaggerates minor ones which he has."

6. A defendant is entitled to have medical experts who have observed the plaintiff's demeanor and reactions on trial of the case take the stand and give any opinion they may have reached concerning presence of conscious malingering. One court has held that an expert cannot describe the plaintiff's demeanor, as the jurors can see that for themselves, but this seems to be an artificial and undesirable restraint, for the trained eye of the medical expert will see significant features which the layman might miss. Furthermore, an expert should always be encouraged to expose the basic facts upon which he rests his opinion.

The reader will see that traumatic neurosis is the flowering stalk of a previously planted seed, the recurrent breaking open of an old scar, the further damaging of a cracked vase so that it will not hold water until mended once again, indeed a veritable Pandora's box full of idiosyncrasies, multiple mechanisms and ambiguous causations. It has taxed the scientific technics of medicine, and we do not wonder that it should have strained the methods of the law now available for fixing a fair compensation.

We said in the beginning that the law-medicine problems which revolve around the traumatic neuroses are vexed and vexatious. We say so again. If we have put forward a useful rationale for orientating the problem of proof, we have gained our goal.

# THE DIETARY FACTOR IN THE ETIOLOGY OF PERNICIOUS ANEMIA \*

By JOHN MARTIN ASKEY, M.D., F.A.C.P., *Los Angeles, California*

ADDISONIAN pernicious anemia is known to develop in accordance with genetic, racial, climatic and geographic determinants. The hypothesis that the disease is of dietary origin has been advanced. If dietary deficiencies cause Addisonian pernicious anemia, they must explain the natural distribution and the natural history of the typical form of the disease.

*The Natural Distribution of the Disease.* Pernicious anemia is geographically distributed. It is rare in Asia, common in Northern Europe, Canada and the Northern United States. It is less common in the Mediterranean and Southern European areas, in South America and Southern United States.

Racially, it is extremely rare in the Asiatics, Negroes and Egyptians. Constitutionally, the light complexioned, fair haired types are susceptible; the pigmented types resistant.<sup>1</sup> There is a tendency to familial grouping in the susceptible races.

Climatically, in the United States, it varies in incidence according to Petersen and Mills,<sup>2a</sup> with the storm track areas. Smith<sup>2b</sup> ascribes the distribution to variation in effective solar radiation.

*What Are the Essential Objective Criteria in Typical Addisonian Pernicious Anemia?* Macrocytic hyperchromic anemia, glossitis, bone marrow and nerve tissue changes are not specific objective criteria. They may be produced by other mechanisms than that producing Addisonian pernicious anemia.<sup>3</sup> They are pathognomonic only when they have been proved to result from a deficiency of the special anti-pernicious anemia liver principle. The essential objective changes in pernicious anemia are those involved in the depletion of this essential liver principle. There are three such constantly associated objective findings in the patient in relapse, permanent histamine refractory anacidity, permanent reduction of Castle's intrinsic factor, and reduction of the stored anti-pernicious anemia liver principle. This appears to represent a primary composite triad of objective criteria, essential in the pathogenesis of the disease. The anemia, bone marrow changes, and nerve changes are secondary developments. Only as composite findings are the three criteria significant. The loss of the intrinsic factor of Castle, although essential, is not, alone, pathognomonic of Addisonian pernicious anemia.

It has been found to be absent in patients who had malignant destruction of the pylorus,<sup>4, 5</sup> in sprue,<sup>6</sup> and in multiple intestinal anastomoses.<sup>7, 8</sup> Castle

\* Received for publication May 21, 1943.

From the Department of Medicine, University of Southern California School of Medicine.

observed the disappearance and return of the intrinsic factor in a patient who had intestinal stenosis.<sup>9</sup> It has been shown to disappear transiently during pregnancy.<sup>10</sup> The manner of its loss, not the loss per se, is its pathognomonic feature in Addisonian pernicious anemia.

Even the loss of the anti-anemic liver principle does not, alone, denote the disease. It can be induced by other mechanisms than that producing Addisonian pernicious anemia. It has been shown to occur with cancer of the pylorus<sup>11</sup> and in sprue.<sup>6</sup>

The mere existence of the triad is not pathognomonic of Addisonian pernicious anemia. It is essential, but it can exist theoretically in other conditions.<sup>6</sup>

The specific features about the triad are its specific chronology of development and the precise relationship of the findings to the disease. The anacidity is invariably present; it is a long standing precursor and is permanently refractory to histamine. The loss\* of intrinsic factor is invariably demonstrable, and is permanent. The triad is constantly associated with no other disease. Although its components may theoretically occur in isolated cases of other diseases, they do not show the above precise characteristics.

*The Natural History of Pernicious Anemia.* The natural history of the development of this essential objective triad suggests a long period of evolution. The chronology is apparently a development in orderly sequence of anacidity, loss of intrinsic factor, and loss of the anti-pernicious anemia liver principle.

The period of anacidity alone represents the potential stage of pernicious anemia, the hazard varying from a negligible one in ordinary individuals<sup>12</sup> to a fairly high one in blood relatives.<sup>13</sup> The time of onset is variable, supposedly congenital in some, but in others it is known to be acquired.<sup>13</sup>

The potential disease enters the latent stage with the onset of reduction of the intrinsic factor. At this period, the fundamental etiologic objective change of the typical disease has occurred. There now exists the defective physiology producing reduction of the specific liver principle.

The active stage, marked by abnormal blood, bone marrow and nerve tissue changes, occurs when the stored anti-pernicious anemia liver principle drops below the critical level necessary for normal hematopoiesis and nerve nutrition.

The successive stages, potential, latent and active, merge into each other without sharp definition, marked by no significant transitional signs or symptoms. The gradual objective changes are apparently reflected in the insidious subjective changes described by Addison. "The patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme." This, then, is the natural history of typical Addisonian pernicious anemia. Definitive data as to the etiologic effect of diet must ade-

\* By the term "loss" is meant that there is insufficient intrinsic factor to produce a significant reticulocyte response by a biologic assay. Goldhamer has shown that a reduction, not a "loss," actually occurs.



quately explain this natural history of development. Anemias which are not produced by this orderly mechanism are not typical pernicious anemia and can be excluded from this study.

The cause of the typical form must be determined before considering the atypical. Anemias without achlorhydria are atypical. Anemias associated with retention of intrinsic factor are not Addisonian pernicious anemia. Anemias in patients who have lost intrinsic factor but not the hydrochloric acid secretion are not typical.

*Can Diet Deficiencies Produce Either Typical Addisonian Pernicious Anemia or the Early Essential Objective Changes in Proper Sequence?* We may approach the problem by asking the following questions:

1. Is the incidence of the disease higher in areas where undernutrition is prevalent?
2. Are the diets prior to the onset of Addisonian pernicious anemia deficient?
3. Do individuals with known, long standing diet deficiencies develop this form of anemia or its essential early criteria?
4. Can dietary deficiencies produce the essential findings in experimental animals?

*Is the Incidence of Addisonian Pernicious Anemia Higher in Areas in Which Undernutrition Is Prominent?* There is no correlation between the natural distribution of the disease and poor nutrition. It is found chiefly among those who use a diet high in protein and meat and are well fed. It is lowest among the people where famine, undernutrition and avitaminoses are common. In China, Yang and Keefer<sup>14</sup> found prior to 1931 only four of 25,000 hospital admissions who had pernicious anemia. In 1941, Snapper<sup>15</sup> said that in the admissions to the Peiping Union Medical College Hospital since 1921, only six patients could be found in whom the diagnosis seemed to be justified. In all six, however, some signs could be found which seemed to distinguish them from real pernicious anemia. He does not believe that they suffered from genuine pernicious anemia. In contrast, in North America three or four in every 1,000 patients admitted to general hospitals are found to have pernicious anemia.<sup>16</sup> In India, where Wills<sup>17</sup> described tropical macrocytic anemia which she attributed to deficient diets, pernicious anemia is practically unknown. There are few authenticated instances.<sup>18</sup> Erulkar<sup>19</sup> speaks of Addisonian pernicious anemia but described no patients. Tropical macrocytic anemia is also prevalent in the Malay States, China and the West Coast of Africa. In these areas, also, pernicious anemia is rare. In Java, all gradations of undernutrition and avitaminosis are always present. If loss of intrinsic factor and development of pernicious anemia were attributable to either acute or chronic undernutrition, it should be reflected in an increased incidence of the disease in Java. De Langen<sup>20</sup> states that during a period of 20 years he did not encounter one patient among the natives.

*Are the Diets Prior to the Onset of Addisonian Pernicious Anemia Deficient?* Few detailed studies of the diets preceding the manifestations of pernicious anemia have been made. Minot and Murphy, in their classic paper in 1926, said: "We have noted it is not uncommon for these patients to have consumed throughout life unusually large amounts of food rich in fats. Patients with pernicious anemia also may give a history of partaking for years of some other type of one-sided diet." Cornell<sup>21</sup> studied the diets used by 26 patients during 10 years before the onset of symptoms and signs of pernicious anemia. He concluded that "on the whole, these individuals have consumed fairly average diets. Their diets, in most cases, were the same over the ten year period as those of their nearest associates, who did not develop pernicious anemia. It is probable, therefore, that pernicious anemia is not due, fundamentally, either to excess or deficiency of any type of food."

Ungley and James<sup>22</sup> studied the diets used by 15 patients preceding the onset of pernicious anemia. Six had used a diet especially deficient in meat and green vegetables. The remaining nine had used diets that appeared to be normal. They found no difference in the preceding diets of those with and without spinal cord lesions.

Unfortunately, dietary histories of patients prior to relapse do not furnish precise data. It cannot be said whether any deficiencies noted preceded or followed reduction of the intrinsic factor. Thus, diet abnormalities found years before relapse still might be due to the anorexia and taste perversions of the early active stage. They might represent concomitants of the early stage and not precursors. The aversion to meat reported by many patients for a variable period is probably an abnormality of the latent and early active stage. There are apparently no precise data upon which any marked diet deficiencies in individuals with Addisonian pernicious anemia may be based, save for the period just before manifestation of the disease.

*Can Dietary Deficiencies Produce Addisonian Pernicious Anemia?* Specifically, can dietary deficiencies cause a loss of the antipernicious anemia liver principle by the mechanism by which it is lost in typical Addisonian pernicious anemia? The nature of the disease precludes any planned human experimentation with prolonged diet restriction. Natural experiments are available, however.

In India, many Mohammedan women live on diets largely vegetarian, high in carbohydrates and low in protein and the vitamin B complex. This produces, in many instances, a macrocytic hyperchromic anemia, but hydrochloric acid is usually retained in the stomach. The anemia does not respond to the Dakin-West anti-pernicious anemia fraction (Anahaemin)\*<sup>23</sup> and, thus, is apparently not due to a deficiency of the specific antipernicious anemia principle. The dietary factor lacking cannot be Castle's extrinsic

\* Anahaemin (British Drug Houses) is an extract prepared by the method of Dakin and West.

factor and the anemia cannot be ascribed to the mechanism which operates in Addisonian pernicious anemia.

In Northern China, Snapper<sup>15</sup> says the diet is generally deficient in protein, calcium, vitamins A, C and D but is sufficient in vitamin B. Here a macrocytic anemia very similar to that occurring in India results, so deficiency in vitamin B cannot be the factor in its production.

In Puerto Rico, diets deficient for years in meat, milk, eggs, whole grain cereals and butter are found prior to the development of sprue.<sup>6</sup> The majority of those with macrocytic anemia retained intrinsic factor sufficient to provoke a significant reticulocyte response after the administration of beef muscle. Loss of Castle's intrinsic factor was demonstrated in two instances by a biologic assay. In one, loss of the anti-anemic liver principle occurred. Hydrochloric acid was retained in the stomach. In the majority of these patients with sprue, there was retention of acid and of intrinsic factor. There was no constant relationship of the essential triad as is found in pernicious anemia. Therefore, in sprue even though certain components of the triad occasionally may be present, they are seldom all present, the characteristic sequence of their development does not occur, and they bear no precise etiologic relationship to the anemia. The deficient diet associated with the production of sprue does not induce a macrocytic anemia which can be explained by the mechanism producing pernicious anemia.

In the Southern United States, diets deficient in calories, protein, calcium, phosphorus and the known vitamins over a period of years lead, not to the development of pernicious anemia, but to pellagra. Macrocytic anemias with loss of hydrochloric acid and Castle's intrinsic factor may occur, but it is not a constant association.<sup>24, 25</sup> The anti-pernicious anemia liver principle was not lost in the one case tested.<sup>26</sup> Achlorhydria occurs in about 70 per cent.

*Response to the Administration of Liver Extract.* The macrocytic anemias of the tropics, of pellagra, and of sprue respond to the injection of liver extract, and for this reason they have been ascribed to a deficiency of the anti-pernicious anemia principle. Cohn's liver fraction G, which is usually employed, contains two distinct anti-macrocytic anemia principles—one the specific-pernicious anemia principle, the other the anti-macrocytic anemia principle effective in tropical macrocytic anemia.<sup>27</sup> Response to the administration of liver extract by injection apparently cannot establish that an anemia is due to deficiency of the specific anti-pernicious anemia principle unless a more purified extract, such as the Dakin-West fraction, is employed.

Tropical macrocytic anemia does not respond to the Dakin-West (Ana-haemin) fraction.<sup>23</sup> Wills described<sup>23</sup> one instance of macrocytic anemia of sprue which did not respond to the administration of the Dakin-West fraction. Such data are meagre, because in most instances treatment is with Cohn's fraction G. Other data suggest that the deficiency causing these anemias is not one of the specific anti-pernicious anemia principle. A much

larger dose of liver extract is needed for nutritional macrocytic anemia, and for the macrocytic anemias of pellagra and sprue than is needed for pernicious anemia in relapse.<sup>28</sup>

Clinically, these macrocytic anemias have more similarities to each other than they have to Addisonian pernicious anemia. They do not show the increased hemolysis of pernicious anemia, nor the frequency of neurologic involvement. Diet deficiencies are common to all, and the character of the deficient diets is similar.

To summarize, deficient diets in man over a period of years may be demonstrated to produce macrocytic anemias, but not commonly by the mechanism operative in Addisonian pernicious anemia. They are apparently not due to deficiency of Castle's extrinsic factor, to loss of the intrinsic factor nor to loss of the specific anti-pernicious anemia principle save in such rare instances that it cannot be of etiologic significance.

Diet deficiencies apparently do not produce either manifest pernicious anemia or the early essential objective changes.

*Can Dietary Deficiencies Produce the Essential Findings of Pernicious Anemia in Experimental Animals?* Dietary observations on experimental animals must face fundamental objections. Pernicious anemia does not occur spontaneously in animals.<sup>29</sup> Similar syndromes are analogues which serve only to direct the study of the human prototype. It is difficult by any means to produce a satisfactory picture of pernicious anemia in an animal which might be used as a test animal for the determination of liver potency.<sup>30</sup> Few lower animals have the same mechanism of production of the anti-pernicious anemia liver substance as is found in man. Only in the hog does the physiology of production of this principle seem similar enough to justify its use as an experimental animal. This similarity is a broad one, however, and cannot be accepted with respect to details without inducing faulty inferences. This has been illustrated by the inference that Castle's intrinsic factor in man was produced in the pyloric glands and Brunner's glands because this was true in the hog. Fox<sup>31</sup> demonstrated by biologic assay that the intrinsic factor in man was probably secreted in the fundus type of gland and not in the "pyloric gland organ" as occurred in the hog.

Only in the hog has the essential triad of objective findings been produced by diet deficiencies.<sup>32</sup> This followed the use of a modified Goldberger-Wheeler diet. The same diet in man, however, does not produce Addisonian pernicious anemia, nor the essential triad. It usually produces pellagra.<sup>33</sup> The same diet in the dog produces black tongue, not the essential triad.

Deficient diets administered to monkeys produce conflicting results. The marked nutritional macrocytic anemia produced by Wills<sup>34</sup> was not analogous to pernicious anemia as it did not respond to refined liver extract effective in man. Bussabarger<sup>35</sup> could not produce a similar anemia in monkeys by a similar diet.

The application of such results obtained on experimental animals to man is confusing rather than illuminating. Diet deficiencies which produce the

essential objective triad of pernicious anemia in the remote species, the hog, fail to produce pernicious anemia either in the nearest phylogenetic species to man, the monkey, or man himself. Results in experimental animals can be of crucial significance only when diets which produce the triad in animals are used in man and produce pernicious anemia. Acceptable data must be based upon example rather than upon analogy.

### DISCUSSION

By correlation of diet with manifest Addisonian pernicious anemia and with the early essential objective criteria, no essential relation can be established between diet deficiency and the incidence of manifest or early Addisonian pernicious anemia. Diet, apparently, is not a factor in initiating the disease. Is the geographical distribution, then, dependent upon climatic or upon racial determinants? In the same climatic environment, there is definite racial difference in the incidence of Addisonian pernicious anemia. Friedlander<sup>1</sup> found this true in Boston. In Java, only the white races develop the disease. Pure blooded negroes do not develop pernicious anemia in the same climate as Caucasians.

Where the racial factor is constant, and the climatic factor is variable, varying results occur.

In China and Japan, although the climate varies radically in Northern and Southern areas, there is no varying effect upon the incidence. There is little or no pernicious anemia in any area in either China or Japan. Pure blooded negroes apparently do not develop pernicious anemia in either the Northern or Southern states in the United States. Among the white races of the United States, however, there is a lower incidence of the disease in those living in the Southern states.

Climate, apparently, is of secondary importance to race in producing the incidence of pernicious anemia. This is probably true, also, of Javanese, East Indians and other Asiatics. These races are relatively immune, regardless of the environment. In other races, exemplified by the white races in the United States, among whom the incidence is relatively high, climate is a factor.<sup>2</sup>

Racial factors best explain the national geographic distribution. Purely racial factors are hereditary factors. If the loss of intrinsic factor is a racial trait, it must be an hereditary trait. Heredity thus emerges as apparently the only adequate explanation for the natural distribution and the natural history of Addisonian pernicious anemia.

An inborn genetic defect is accepted as the cause of loss of intrinsic factor in many individual instances. The reluctance to accept this as the cause of all pernicious anemia has been due to an inability to demonstrate it as the cause in certain individual instances, and the uncertainty as to the parts played by race, diet, climate and geography.

Inability to demonstrate a family pedigree in an individual patient con-

stitutes no valid objection to the theory of hereditary transmission. A recessive gene carrying a genetic fault may pass undetected through an unlimited number of generations. Hereditary predisposition would appear to be responsible for the disease both in certain races and in certain individuals.

The following hypothesis for the genetic origin of Addisonian pernicious anemia seems compatible with the available data.

Faulty genes tending toward loss of Castle's intrinsic factor are apparently distributed in varying quantities in different races. The genotype in a rigorous climatic environment loses gradually the intrinsic factor but tends to retain it in warmer climates. Dietetic external conditions have no effect upon the rate of development of this loss. During the gradual depletion, however, a diet rich in extrinsic factor may postpone or a diet containing a frequent ration of liver may prevent the manifestations of the active stage of the disease.

Since liver is rarely a constant dietary ingredient, those individuals with the genotype for pernicious anemia eventually will manifest the disease if they live long enough. In the races where the genetic fault is comparatively common, the hereditary nature is evidenced by a frequent increased familial incidence, and a tendency toward a constitutional or hereditary type.

The acceptance of heredity as the cause of Addisonian pernicious anemia would make a program for the prevention of the disease feasible. The potential cases should be found among the blood relatives with achlorhydria.<sup>13</sup> Grouping of all blood relatives by the histamine gastric analysis into those with acid and those without acid would identify the vast majority of the genotypes who later will develop the disease.

### CONCLUSIONS

1. Diet deficiencies cannot account satisfactorily for the production of Addisonian pernicious anemia.
2. The natural distribution, which is racial, geographic and climatic, can be adequately explained by hereditary factors.
3. An active program for prevention is thus justified by which potential cases may be sought among blood relatives.

### BIBLIOGRAPHY

1. FRIEDLANDER, R. D.: Racial factor in pernicious anemia; study of 500 cases, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 634-642.
2. (a) PETERSEN, W. F.: The patient and the weather, vol. 1, part 1, 1935, Edwards Brothers, Inc., Ann Arbor, Michigan, page 75.  
MILLS, C. A.: Geographic or climatic variations in death rate from pernicious anemia, exophthalmic goitre, Addison's disease and angina pectoris, *Arch. Int. Med.*, 1930, xli, 741-751.  
(b) SMITH, J. H.: Relation between deficiency of solar radiation and mortality due to pernicious anemia in the United States, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 200.
3. MANSON-BAHR, P. H.: Glossitis and vitamin B<sub>12</sub> complex in pellagra, sprue, and allied states, *Lancet*, 1940, ii, 317, 356.

- MANSON-BAHR, P. H.: Treatment of sprue with vitamin B<sub>12</sub> and its bearing upon the aetiology of this disease, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1941, xxxiv, 347-372.
- RHOADS, C. P., and CASTLE, W. B.: Pathology of bone marrow in sprue anemia, *Am. Jr. Path.*, (supp), 1933, ix, 813-826.
- WOLTMAN, H. W., and HECK, F. J.: Funicular degeneration of the spinal cord without pernicious anemia; neurologic aspects of sprue, non-tropical sprue and idiopathic steatorrhea, *Arch. Int. Med.*, 1937, lx, 272-300.
4. GOLDHAMER, S. M.: Macrocytic anemia in cancer of the stomach, apparently due to lack of intrinsic factor, *Am. Jr. Med. Sci.*, 1938, cxcv, 17-20.
  5. STURGIS, C. C., and GOLDHAMER, S. M.: Macrocytic anemia, other than pernicious anemia, associated with lesions of the gastro-intestinal tract, *ANN. INT. MED.*, 1939, xii, 1245-1262.
  6. CASTLE, W. B., RHOADS, C. P., LAWSON, H. A., and PAYNE, G. C.: Etiology and treatment of sprue, *Arch. Int. Med.*, 1935, lvi, 627-699.
  7. CASTLE, W. B., TOWNSEND, W. C., and HEATH, C. W.: Further observations on the aetiological relationship of achylia gastrica to pernicious anaemia, *Lancet*, 1930, i, 1062-1063.
  8. BARKER, W. H., and HUMMEL, L. E.: Macrocytic anemia in association with intestinal strictures and anastomoses; review of the literature and report of two new cases, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 215-256.
  9. Year Book of General Medicine, 1933, Editorial note, page 341.
  10. STRAUSS, M. B., and CASTLE, W. B.: Studies of anemia in pregnancy; the etiologic relationship of gastric secretory defects and dietary deficiency to the hypochromic and macrocytic (pernicious) anemias of pregnancy and the treatment of these conditions, *Am. Jr. Med. Sci.*, 1933, clxxxv, 539-551.
  11. SCHENKEN, J. R., STASNEY, J., and HALL, W. K.: Antianemic principle in human liver in carcinomas of stomach and cecum, *Am. Jr. Med. Sci.*, 1940, cc, 11-17.
  12. BLOOMFIELD, A. L., and POLLAND, W. S.: Fate of people with unexplained gastric anacidity; follow-up studies, *Jr. Clin. Invest.*, 1935, xiv, 321-324.
  13. ASKEY, J. M.: Prevention of pernicious anemia; recognition of latent stage in relatives, *ANN. INT. MED.*, 1940, xiv, 593-607.
  14. YANG, C. S., and KEEFER, C. S.: Pernicious anemia in Chinese patients; report of case, *Nat. Med. Jr. China*, 1931, xvii, 218-223.
  15. SNAPPER, I.: Chinese lessons to western medicine, 1941, Interscience Publishers, Inc. New York, page 284.
  16. STURGIS, C. C.: Diseases of the blood, in: MUSSER, J. H.: Internal medicine, 4th edition, 1940, Lea and Febiger, Philadelphia, page 947.
  17. WILLS, L., and MEHTA, M. M.: Studies in "pernicious anaemia" of pregnancy; preliminary report, *Indian Jr. Med. Res.*, 1930, xvii, 777-792.
  18. SPAAR, E. C.: Pernicious anaemia in an Asiatic, *Brit. Med. Jr.*, 1934, i, 578-579.  
TAYLOR, G. F., and CHITKARA, N. L.: Report of two post-mortems and five cases of Addisonian pernicious anaemia, *Indian Med. Gaz.*, 1940, lxxv, 16-19.
  19. ERULKAR, A. S.: Pernicious anaemia in India, *Clin. Jr.*, 1931, lx, 237-238.
  20. DE LANGEN, C. D.: Studies in blood diseases and blood regeneration in Java, *Proc. Roy. Soc. Med.*, 1933, xxvi, 763-772.
  21. CORNELL, B. S.: Study of pre-disease diets of patients with pernicious anaemia, *Bull. Johns Hopkins Hosp.*, 1927, xl, 409-421.
  22. UNGLEY, C. C., and JAMES, G. V.: Effect of yeast and wheat embryo in anaemias; nature of haemopoietic factor in yeast effective in pernicious anaemia, *Quart. Jr. Med.*, 1934, iii, 523-548.
  23. WILLS, L., and EVANS, B. D. F.: Tropical macrocytic anaemia: its relation to pernicious anaemia, *Lancet*, 1938, ii, 416-421.
  24. SPIES, T. D., and PAYNE, W.: Study of the etiological relationship between pellagra and pernicious anemia, *Jr. Clin. Invest.*, 1933, xii, 229-234.

25. SALAH, M.: Demonstration of haemopoietic principle in chronic pellagric achylia, *Trans. Roy. Soc. Med. and Hyg.*, 1935, xxix, 299-302.
26. SYDENSTRICKER, V. P., SCHMIDT, H. L., JR., GEESLIN, L. E., and WEAVER, J. W.: Liver in pellagra, *Am. Jr. Med. Sci.*, 1939, cxcvii, 755-763.
27. WILLS, L., CLUTTERBUCK, P. W., and EVANS, B. D. F.: New factor in production and cure of certain macrocytic anaemias, *Lancet*, 1937, i, 311-314.
28. TROWELL, H. C.: Liver extract in treatment of tropical macrocytic anaemia, *Lancet*, 1941, ii, 303-304.  
SPIES, T. D.: Observations on the treatment of pellagra, *Jr. Clin. Invest.*, 1934, xiii, 807-816.  
RHOADS, C. P., and MILLER, D. K.: Intensive liver extract therapy of sprue, *Jr. Am. Med. Assoc.*, 1934, ciii, 387-391.
29. HUTYRA, F., MAREK, J., and MANNINGER, R.: Special pathology and therapeutics of the diseases of domestic animals, 4th English edition, volume 3, 1938, Alexander Eger, Chicago, page 101.
30. GEIGER, A. J., GOODMAN, L. S., and CLAIBORN, L. N.: Effects of gastrointestinal resections in swine on anti-anemia potency of liver, with observations on nature and sources of materials effective in pernicious anemia, *Yale Jr. Biol. and Med.*, 1940, xiii, 259-278.
31. FOX, H. J., and CASTLE, W. B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia, *Am. Jr. Med. Sci.*, 1942, cciii, 18-28.
32. MILLER, D. K., and RHOADS, C. P.: Experimental production of loss of hematopoietic elements of gastric secretion and of liver in swine with achlorhydria and anemia, *Jr. Clin. Invest.*, 1935, xiv, 153-172.
33. GOLDBERGER, J., and WHEELER, G. A.: Experimental production of pellagra in human subjects by means of diet, *Hygienic Lab. Bull., U. S. P. H. S.*, 1920, No. 120, 7-116.
34. WILLS, L., and BILIMORIA, H. S.: Studies in pernicious anaemia of pregnancy; production of macrocytic anaemia in monkeys by deficient feeding, *Indian Jr. Med. Res.*, 1932, xx, 391-402.  
WILLS, L., and STEWART, A.: Experimental anaemia in monkeys, with special reference to macrocytic nutritional anaemia, *Brit. Jr. Exper. Path.*, 1935, xvi, 444-453.
35. BUSSABARGER, R. A., IVY, A. C., WIGODSKY, H. S., and GUNN, F. D.: Effect of gastrectomy on the monkey, *ANN. INT. MED.*, 1939, xiii, 1028-1041.



## PSYCHOTHERAPY \*

By S. KATZENELBOGEN,† M.D., F.A.C.P., *Washington, D. C.*

PSYCHOTHERAPY may be defined as treatment by means which appeal to both intellectual and emotional functioning of the individual. It uses procedures which require special knowledge and training. In addition to, but also independently of such procedures, psychotherapy makes use of and is inadvertently influenced by factors involving the therapist, other persons in contact with the patient, and events affecting him. This definition implies that psychotherapeutic influences may be present in any medical treatment, in any relationship of the patient with others, in anything he is subjected to or comes in contact with, insofar as such varied relationships, things, and events somehow affect the patient. Such a broad definition necessarily postulates that aside from psychotherapy as practiced by specialists, psychotherapy is being carried out on a much larger scale by physicians practicing any branch of medicine, by psychologists, educators, social workers, nurses, and others coming in contact with the patient, although they may not intend to use and remain unaware of using psychotherapy.

*Is Psychotherapy an Art or a Science?* The answer is that it is both. And so it may be added, is any other medical treatment and the practice of medicine itself. The vast application of psychotherapeutic influences, whether used knowingly or not, and the varied success attained by the uninitiated account for the much credited contention that it is an art; further arguments in favor of its being an art point out that it deals with so-called "intangible elements" of the human organism. Of course, intellectual and emotional reactions of a person are different from physiological reactions, the latter being, so to speak, palpable physical phenomena. Psychological reactions are nonetheless observable and lend themselves to study just as comprehensively as many a physical or chemical phenomenon. Bear in mind that human beings form an opinion of the prevalent personality traits and modes of behavior of their friends. On the basis of their knowledge acquired from observation they have a pretty accurate idea of how those friends might react under certain known circumstances. It is obvious, however, that in the practice of psychotherapy, as in that of any other field of human endeavor and activity, *aside from knowledge and experience, the personal equation of the therapist plays a rôle which cannot be too strongly emphasized.* Not all those trained similarly in the same surgical clinic turn out to be surgeons of the same ability. So it is, generally speaking, with psychotherapists. Adequate or inadequate application of psychotherapy in individual cases will be determined not only by the extent of the experience

\* Received for publication August 17, 1943.

† Clinical Professor of Psychiatry, George Washington University School of Medicine, Washington, D. C.

and knowledge of the psychotherapist but also by his skill in making use of his experience and knowledge.

*Scope of Psychotherapy.* Although the aim of psychotherapy and its procedures is psychological in nature, it does not follow that so-called physical diseases, i.e., abnormal functions of organs, are outside its domain. Insofar as certain somatic disorders of functional origin are recognized to be of psychogenic origin, the rational therapy in such instances will be the one which aims primarily to treat the cause—the abnormal function of the person—rather than essentially the result, i.e., the abnormal function of organs. Moreover, even in certain of the so-called organic-structural diseases, psychotherapy may be a useful adjunct for the reason that disturbed function of organs affects more or less the intellectual and emotional functioning of the person—the host of the physical disease. Thus, the field of psychotherapy is not limited to psychiatry—to treatment of psychotic and psychoneurotic patients. It should be included in the therapeutic armamentarium of medicine—in the treatment primarily of physical diseases of psychological origin and also, within certain limits, of organic-structural diseases.

*Problems.* Two sets of problems face the psychotherapist: (a) Medical problems, and (b) problems deriving from the interrelationships between the patient and his immediate environment or community. Although it is not possible to draw a clear-cut demarcation between these two types of problems, nevertheless, they offer distinct points which need special emphasis.

1. The medical problems include complaints by the patient regarding his physical or mental health or both. In certain instances the sole or main complainer will be not the patient but those in contact with him, the emphasis being on the trouble caused by the patient's behavior to others in his environment. However, the outstanding common feature of the complaints either by the patient or by those in his environment, or by both, is that they are centered on the patient's health. Whatever opinion is prevalent as to the causal relationship between the ill health of the patient and his position in the environment, the fact remains that neither the patient nor his relatives and friends nor others in contact with him bring forth human relationships as a special problem.

2. The other problems with which the physician-psychotherapist must cope include human relationships as the central issue, though there may also be bodily complaints. The patient himself, although feeling healthy in every respect, complains of being unsuccessful in school or in his occupation, of being unpopular, of not being able to adjust adequately in his family and in his social relationships outside his home. He may or may not recognize his own faulty behavior; he may shift the blame wholly or in part to others, and in this he may be not wholly incorrect. In other instances the patient himself feels well and contented, but his behavior, attitudes, whether he recognizes it or not, make life uncomfortable for those around him. Those others, however, or some of them at least, may be not wholly correct in

blaming the patient entirely and not finding any fault whatsoever with themselves.

Thus the psychotherapist, whether he deals only with essentially medical problems or with problems apparently involving only social relationships, must bear in mind two possibilities: The one is that even though the patient's difficulties are wholly concentrated on his bodily feelings, his family and social relationships may also be potent factors. The other possibility is that in case the whole emphasis is laid on the patient's inadequate social relationships, or whenever the social relationships of the patient present a problem at all, one must not forget that in any relationship there are at least two partners. One of the prerequisites of adequate psychotherapy, therefore, is to bear in mind the possibility that under certain circumstances the treatment of the patient cannot be expected to be successful unless and until it is supplemented by changing his position in the environment or by trying to take care of the inadequacies in the environment.

*Modes of Approach of Psychotherapy.* The ultimate goal of psychotherapy is to attack the very cause of the patient's difficulties. It aims, therefore, to derive its methods from the etiologic and pathogenetic concepts prevalent in psychopathology. Like medical treatment, psychotherapy aims to be etiologic and pathogenetic or genetic-dynamic in the psychiatric parlance. However, etiologic and pathogenetic treatment, being necessarily restricted by limitations in our knowledge of etiology and pathogenesis, must yield to other less ambitious modes of treatment. For the sake of an orderly discussion, I suggest treating the varied psychotherapeutic procedures under two headings:

I. Non-Specific Psychotherapy

II. Specific or Genetic-Dynamic Psychotherapy

*I. Non-Specific Psychotherapy.* As the term suggests, this therapeutic approach aims to relieve the patient of his troubles, as far as possible, without claiming to attack specifically the roots of the evil. To use an analogy, this therapeutic approach is comparable to the so-called symptomatic treatment in medicine, although the guiding principles of the two therapies are totally different. Medical treatment aims to treat the abnormal function of organs, or to build up the physical resistance of the organism or to do both; psychotherapy directs its means of attack solely toward the mental functioning of the person, regardless of the apparent nature of the disorders—physical or mental. Non-specific psychotherapy uses various procedures, to all of which applies at least one common denominator, i.e., the absolute prerequisite of good rapport between the psychotherapist and the patient. In this patient-physician relationship the partners are not equals; it is a relationship of a weak person who seeks the help of a strong one. The patient believes in the superior knowledge and ability of the physician he chooses to help him. This faith creates a very fertile background for mental influences.

With this preparedness of the patient to receive those influences, the physician has the opportunity to exercise his ability to affect the intellectual and mental functioning of the patient. This is being accomplished through various ways and means, some of which operate even without the active participation of the psychotherapist. Thus the very fact that the patient is aware of the accessibility of the care he wants is apt to have a beneficial effect. Furthermore, any happening which will heighten the prestige of the therapist outside his actual contact with the patient will also strengthen the passive beneficial influence of the former on the latter. When the patient faces the psychotherapist, another also rather passive factor is therapeutically effective. I allude to the therapist's attentive and sympathetic listening to the patient's story of his difficulties. The benefit the patient gets from this phase of contact with the therapist may be attributed to several factors: The therapist's desire to understand the substance and nature of the patient's troubles and, above all, his recognition of the reality of these troubles, in contrast with the attitude of those who heretofore have shown the patient, explicitly or implicitly, unmistakable evidence of their feelings that his troubles were more imaginary than real. This display of respect, understanding, and a humane sympathetic attitude by the psychotherapist—"who knows better"—toward an individual who is burdened with feelings of inadequacy, who is a weakling insofar as alone he cannot cope with his difficulties, has tremendous therapeutic potentialities. In the process of recounting the story of his troubles the patient finds a certain relief from emotional tension. And last but not least,—still in the phase of passive psychotherapy—from these various factors, each of which has its relative therapeutic value, the patient derives hope, another very potent therapeutic agent.

This part of the psychotherapeutic contact, called, somewhat artificially and only for didactic purposes, the passive part of psychotherapy (attentive listening by the therapist to the patient's story and his attentive attitude toward the patient constitute action), is accompanied and followed by the therapist's more active participation. The tools used in the active phase of non-specific psychotherapy will be only mentioned here: Reassurance, persuasion, suggestion, and the extreme degree of suggestive action, hypnosis.<sup>1, 2, 3</sup> It should be pointed out, however, that hypnosis in certain of its aspects (as an adjunct therapeutic procedure) belongs rather to the specific (genetic-dynamic) psychotherapy.

To reemphasize the essential factors entering into the non-specific psychotherapy, my description of the latter begins with the statement that procedures it uses require, first of all, good rapport between the psychotherapist and the patient. Two factors determine its establishment, the one being with the patient and the other with the therapist. The patient must willingly accept the treatment and be receptive of mental influences, reassurance, persuasion and suggestion. Suggestibility, an average normal human trait, becomes abnormal in both of its extremes—above and below the average.

For the purpose of non-specific psychotherapy, suggestibility above that of the average run-of-the-mill person is useful. Although it is a characteristic personality trait, it is important to bear in mind that it is apt to be strengthened or weakened by another factor which rests with the therapist. The latter must inspire in the patient, and also in others in contact with the patient, respect and authority. The higher the therapist's professional standing and his prestige in the community, the greater his chances to have an influence on the intellectual and emotional functioning of his patient. Moreover, he must be able to impress the patient as being not solely and not essentially interested in the "case" in a detached, scientific manner, but his attitude must convince the patient that his physician has the best human feelings for the patient's suffering and that his sole object is to help him. This combination of professional authority and sympathetic attitude on the part of the psychotherapist plus a patient who is a willing and capable recipient of mental influences constitute the ideal background for psychotherapy, more especially the so-called non-specific form. Unfortunately, like many other good things in life, these very ideal conditions for successful psychotherapy also contain the seeds for reverses, apt not only to jeopardize the reasonably expected good therapeutic results but also to create new troubles or to magnify the existing ones. I allude to what may be called "Negative Psychotherapy."

*Negative Psychotherapy.* Because of the confidence of the patient in the professional expertness of the physician, confidence strengthened by the affective component in their relationship, the physician must constantly be on his guard, i.e., he must always remember that whatever he does or says is apt to have an impact on the patient. One very serious difficulty in the therapist's position lies in the fact that, as in any other human relationship, his similar mode of behavior under similar circumstances may impress various patients and relatives in entirely different, albeit, opposite ways. Unfortunately it does happen now and then that the irreproachable, highly qualified behavior of the physician produces entirely unexpected adverse effects on the patient, either directly or through the criticism of the relatives and friends of the patient. A colleague of mine of a very high academic standing and equally high professional reputation, in the rôle of a consultant, took great care in carrying out a very comprehensive physical examination which consumed more time than an average ordinary physical examination does. The patient's immediate reaction was that the "professor" did not feel sure of himself; otherwise, it would not take him so long to carry out the examination. The effect of the physician's attitude on the patient, faultless and even praiseworthy as it may be, depends not on his attitude alone but also on the personality make-up of the patient and of those close to him. However, experience shows instances in which the physician's behavior is manifestly at fault and has definitely harmful effects on the patient. One speaks in such instances of "iatrogenic diseases," i.e., functional disorders of psychogenic

origin for which the physician is to be blamed.<sup>4</sup> By that one means that certain remarks made by the physician to highly suggestible individuals are responsible for causing or protracting complaints of various illnesses. Here the reader's attention is called to the following galaxy of physician's remarks to patients: "You should never go out on the street alone. You may collapse any minute." "Your arteries are slightly hardened." "Your aorta is a little enlarged." "Touch of TB." "Your heart is small." "Grumbling appendix." "Slightly raised blood pressure." "Flabby heart." "Instead of a heart you have a piece of fluttering cheese cloth." "The cells of your stomach are dead." "Neurotic," "psychoneurotic," "psychopathic," "neuropathic," "inferiority complex," "mother fixation." Whatever significance those terms might have had to the doctors who used them, they were accepted by those concerned as meaning disease. These allegorical and metaphorical expressions testifying to a sense of humor, imagination, and literary ability of their authors certainly were used under inappropriate circumstances and indeed had adverse effects on their patients.

II. *Specific—Genetic—Dynamic—Psychotherapy*. By definition this treatment is expected to derive from the knowledge of the "dynamics" or "mechanisms"; i.e., the knowledge of the cause or causes of the illness and their mode of action. This definition needs to be supplemented by the statement that it is not enough and not even the essential thing that the therapist alone feels that he knows the dynamics. It is, in addition, absolutely necessary that the patient himself accept intellectually and experience emotionally what appears to be the causative dynamic factors, that he, so to speak, relive the experiences which had become the genetic-dynamic factors of his troubles. The question arises, how does one go about it in eliciting the dynamic material? How does one proceed to make the patient face his past experiences, to make him grasp and feel their significance in his present troubles? The choice of the method will be determined by the therapist's concepts of psychopathology. The therapist who holds the view that only those experiences in the past life, and particularly the experiences of early childhood, which the patient apparently has completely forgotten, are the essential dynamic factors will regard Freud's psychoanalysis as offering the most significant psychopathological concepts and the free association technic as the only valid and thorough therapeutic method. On the other hand, the therapist who has the conviction that experiences occurring in any phase of the life of the patient may become potent dynamic factors in his illness will choose the method of studying the patient throughout his life. The study will deal with life experiences of which the patient is more or less completely aware and those of which he becomes aware in the process of discussion of events, experiences which may or may not have any apparent connection with the seemingly forgotten experiences. It will also deal with those emotionally colored thoughts, desires, strivings which may be only faintly recognized and not accepted by the patient and which sometimes become, so to speak,

revealed to him through his dreams. In short, the two types of the genetic-dynamic psychotherapies derive from the concept that the present difficulties of the patient are determined by his past life experiences. The very essential difference between them lies in the fact that one type relies essentially if not exclusively on experiences buried in the unconscious, and the other relies essentially on either spontaneously conscious life experiences or those which can be brought into consciousness through discussion. Thus, to reach their aim, the two types of therapeutic procedures have to analyze the mental functioning of the patient, i.e., their tool is analysis of the psyche. However, the term "psychoanalysis" is generally identified with a special technic—the so-called free association technic. The therapist who analyzes the mental functioning of the patient, in other words, who does psychoanalysis without using the special free association technic, has no trade name to offer which would adequately convey the very essence of his therapeutic procedure. The term "distributive analysis" <sup>3</sup> is certainly not telling. It would seem rational to apply the terms "psychoanalysis" and "psychoanalytic" treatment to any therapeutic procedure which tries to influence both the intellectual and emotional functioning of the patient through a study, *an analysis*, of his personality function, i.e., reactions to experiences throughout his life, experiences of which he is aware or unaware. One may further be more specific in making a distinction between: 1. Genetic-dynamic psychotherapy which makes use of the free association technic.<sup>1,2</sup> 2. Genetic-dynamic psychotherapy which makes use of the personality study, i.e., the study of the function of the person throughout his life under varied circumstances.<sup>3, 5</sup>

For current use the following terms are suggested:

1. Psychotherapy with the use of the free association technic.
2. Psychotherapy with the use of the personality study.

*Psychotherapy Which Makes Use of the Personality Study.* Only broad, general principles will be outlined here.

This type of psychotherapy finds a sound background in Meyer's teaching of psychobiology. Rennie in his recent formulation correctly called this type of treatment psychobiological therapy.<sup>5</sup> Its procedure consists essentially in discussing with the patient not only his complaints and problems for which he seeks the help of the therapist, but also varied problems and topics, some of which obviously are related to his difficulties, whereas others have no apparent connection with them. It should be noted that whatever the topics might be, their discussions have one common goal: to further the study by the patient himself of his modes of reactions to life experiences. To begin with, the discussion deals directly with and centers on the complaints and problems formulated by the patient himself and by those in close contact with him. In certain instances, the therapist will be faced chiefly with complaints by others rather than by the patient himself. On the other hand, the patient may be right in his conviction that the difficulty lies not with

him but rather with those who complain about him. Sometimes the environment, although in itself not unusual, is one that does not click with certain personality trends of the patient—his idiosyncrasies, susceptibilities, modes of acting—which again by themselves cannot be considered as being much beyond the normal range of human reactions. One of the tasks of the therapist may then be to deal with the environment, by changing its attitude toward the patient or by removing the patient from an environment unwholesome for him. I suggest that in so handling the situation, one accomplishes an important part of genetic-dynamic therapy, inasmuch as an attempt is made to bring about the patient's recovery or improvement by trying to affect the cause or causes of his difficulties or at least certain factors contributing to them. In most cases, however, whether or not the environment of the patient is to be blamed as an adverse contributing factor, there must be something wrong with the patient himself, since, although he cannot take it, cannot find a *modus vivendi* in his environment, yet he does not attempt to free himself from it, or is unable to do so.

The problems the psychotherapist has to cope with are not only those of maladjustment. The mutual relationship between the patient and his environment may not give rise to complaints from either side. The patient's behavior may be such that it does not in any way adversely affect his environment, nor is the latter objectionable to the patient. Nevertheless, while carrying out his daily activities adequately and behaving satisfactorily, the patient himself may be the sole sufferer, being badly in need of medical and psychiatric help. The necessary conclusion to be drawn from the statements made thus far is that it is the therapist's duty first and foremost to try to learn as much as possible about the complaints and problems involved as they concern both the patient and his environment; i.e., to obtain as comprehensive a history as possible, gathering information not only from the patient but also from whatever source information may be available.

*Taking the History of the Illness and Psychotherapeutic Interviews.* In the discussion of the non-specific psychotherapy, it was pointed out that the establishment of good rapport between the therapist and the patient is a *sine qua non* for any type of psychotherapy. Psychotherapy based on personality study requires the patient's willingness and readiness for a determined effort to take an active part in the treatment. He must be willing to discuss not only his complaints and immediate problems but also experiences and events of the more or less remote past. It is reasonable to admit a priori that the patient will not care to bring forth certain of his experiences, that he will try to omit certain events, that he will be cautious to avoid discussion of situations which might lead to revelation of material which he wants to remain in oblivion, or he will not discuss certain events for the reason that he is not fully aware of them. If the patient is brought to recognize that his being an active partner in the discussions directed by the therapist is essential for the success of the treatment, it is to be expected that he will get interested



in such discussions. One can hardly expect, however, that the patient's interest will be greatly aroused if the therapist takes a detached matter-of-fact attitude without impressing the patient that he is vitally interested—as he actually should be—in the topics he or the patient brings forward for discussion. It follows that the taking of the history marks the beginning in the establishment of the necessary adequate patient-physician relationship and traces the pathway for its further development. The scope of the history is much wider; it gives the patient the opportunity, in recounting the story of his life, to become aware of and feel certain experiences which prove to be significantly revealing to the patient himself; it also opens avenues for further therapeutic sessions, insofar as certain events, personal experiences brought forth in the history, may be taken up for more comprehensive discussions with the patient for the purpose of treatment. Thus, the taking of the history is part and parcel of the personality study and the first step in the psychotherapeutic situation.

The discussion in subsequent psychotherapeutic sessions of the mode of application of the general principles thus far dealt with is beyond the scope of this paper.

#### BIBLIOGRAPHY

1. LEVINE, MAURICE: *Psychotherapy in medical practice*, 1942, Macmillan Co., N. Y.
2. SCHILDER, PAUL: *Psychotherapy*, 1938, W. W. Norton Co., Inc., N. Y.
3. DIETHELM, OSKAR: *Treatment in psychiatry*, 1936, Macmillan Co., N. Y.
4. KATZENELBOGEN, S.: Iatrogenic factors in diseases, *Dis. Nerv. System*, 1941, ii, 342-345.
5. RENNIE, T. A. C.: Psychobiological therapy, *Am. Jr. Psychiat.*, 1940, xcvi, 611-622.

# IMPENDING MYOCARDIAL INFARCTION \*

By LEO WAITZKIN, M.D., *Baltimore, Maryland*

IN 1937 Feil,<sup>1</sup> and Sampson and Eliaser<sup>2</sup> described "preliminary" or "premonitory" pain in 15 (50 per cent) and 29 (48.1 per cent) † of their cases of acute myocardial infarction.

Since this subject is deemed of considerable importance, we are recording our experience and impressions. Of 61 consecutive cases of acute infarction treated in the past two years, 17 had premonitory symptoms. They are summarized in table 1. Additional data are given in 5 cases.

The symptoms have the following characteristics:

1. There may be one or more episodes of spontaneous prolonged cardiac pain, mild or severe, with or without a preceding history of coronary artery disease.

2. Cardiac pain of short duration, on customary or no exertion, suddenly appears where none existed before.

3. In patients with preëxisting angina pectoris, cardiac pain appears on rapidly decreasing amounts of exertion or at rest.

Symptoms precede infarction by a few hours, days, or weeks. Individual attacks of pain last minutes to hours. In one instance, pain lasted seven days. The attacks are considered to be the result of ischemia caused by occlusion or rapid narrowing of a coronary artery, with probable intermittent reflex vasoconstriction of other arteries to explain apparent inconsistencies in the response of pain to effort (cases 13 and 16).

During this preliminary period, physical examination, blood pressure, temperature, and leukocyte count are unchanged. Electrocardiographic abnormalities may be found, which may be due to previous myocardial damage of some duration; but there may be S-T and T-wave contours suggesting recent change (figure 1; and Feil's article, case 15). The electrocardiogram may be perfectly normal. A normal record does not rule out impending myocardial infarction.

While experiencing symptoms premonitory of another infarction, two of our cases, convalescing from an acute attack, had electrocardiograms showing progressive changes toward normal until the second infarction occurred (cases 13, 14; figures 1, 2). The third tracing in figure 1 might be interpreted as showing changes suggesting fresh myocardial activity.

In three cases summarized below, we had interpreted all the symptoms as premonitory in nature and evidence of acute infarction came as a surprise (cases 4, 13, 14).

\* Received for publication April 16, 1943.

From the Medical Service, U. S. Marine Hospital, Norfolk, Virginia.

† The validity of this percentage is questioned, since it is not based on the total number of cases, but on an unstated fraction—27 cases.

TABLE I

Case	Blood Pressure	Past History of Coronary Disease	Interval Between Onset of Preliminary Pain and Infarction	No.	Duration of Preliminary Attacks	Circumstances	Circumstances of Infarction
1	140/90	—	3 hours	1	15 min.	Sleep	After awakening
2	140/82	Effort angina 20 months	5 hours	C.20	10 min.	Began after strenuous activity; recurrent, spontaneous for 5 hours	In bed
3	120/78	Effort angina 4 years	12 hours	Many	"Brief"	Recurrent spontaneous throughout day of usual activity	Immediately after anginal seizures
4	102/62	Effort angina 2 years; worse, 3 months	2 days	2	"Brief"	Spontaneous, promptly relieved by nitroglycerine	Apparently occurred during spontaneous, anginal episodes or was "silent." EKG normal one week before
5	124/86	Effort angina 1 month	2 days	C.30	3 min.	Spontaneous, recurrent for 3½ hours	At rest
6	140/100	Infarct, 1 year previously	3 days	2	4 hrs.	Sleep	Sleep. EKG normal on entry 8 hrs. after onset; similar to EKG taken 1 yr. before. Acute changes during next 3 weeks (figure 4)
7	160/98	—	5 days	4	5-10 min.	Following usual mild activity after noon meals	Sleep
8	148/84	Infarct, 15 months previously	7 days	3	15-30 min.	Usual mild activity	Sleep
9	165/110	Infarct, 2 years previously	7 days	1	7 days	Spontaneous	At rest
10	135/92	Effort angina 20 years	10 days	4	20-90 min.	Spontaneous and sleep	Sleep

TABLE I—Continued

Case	Blood Pressure	Past History of Coronary Disease	Interval Between Onset of Preliminary Pain and Infarction	No.	Duration of Preliminary Attacks	Circumstances	Circumstances of Infarction
11	130/80	—	12 days	Occasional	"Minutes"	Mild effort, sleep	Mild activity
12	108/70	—	20 days	12	"Brief"	Increasingly severe on mild effort	After 3 days partial restriction; died in 7 hours
13	130/80	Infarct within 10 days before	20 days (?)	Many	5-30 min.	Mild effort, spontaneous	After 10 days strict bed rest
14	140/110	Effort angina 2 years	c.1 month	Many	"Brief"	On decreasing activity; 1 spontaneous, $\frac{1}{2}$ hr.	After 5 days complete bed rest
15	140-85	—	35 days	Many	"Brief"	Increasingly frequent on less exertion, occasionally spontaneous	Upon fully clothing himself; after 1 month's intermittent partial and total bed rest
16	120/80	—	35 days	3	"Minutes"	Effort and spontaneous	After partial restriction for 13 days. While undressing. Died in 60 hours
17	124/84	—	35 days	Many	10-15 min.	Increasingly frequent on less exertion. Twice during sleep.	During usual mild activity

Of the 17 cases, infarction followed five hours after strenuous activity in one (case 2); during or after usual mild activity in six (cases 1, 3, 11, 15, 16, 17); during rest in six (cases 4, 5, 9, 12, 13, 14); and during sleep in four (cases 6, 7, 8, 10).

Of two placed at complete bed rest, infarction occurred on the fifth and tenth days (cases 13, 14). Of two at bed rest with bathroom privileges, infarction occurred at rest on the first and third days (cases 4, 12). In one, infarction occurred after 13 days of moderate restriction of activity (case 16).

Of the 17, two died—seven and 60 hours after severe infarction (cases 12, 16). Of the other 44, eight died.

After acute infarction has happened, it is easy to reconstruct the premonitory symptoms and to evaluate them correctly. When confronted with a suspected case, however, the problem is more difficult. Five possibilities exist.

(1) Infarction may not develop at all, and without treatment. This may occasionally happen when there has been an isolated, prolonged, spontaneous cardiac pain in a case of angina pectoris of some standing.

(2) Infarction may have already recently occurred.

(3) Infarction may possibly be averted by treatment.

(4) Infarction will develop regardless of what is done, but conceivably may be minimized.

(5) Infarction may not develop for several weeks after the occurrence of premonitory pains, so that one's suspicions are lulled and treatment relaxed.

That infarction may sometimes be avoided by restricting activity in suspected patients is open to speculation, since there is no way of knowing that it might otherwise have occurred. We have had, however, several patients whose threatening symptoms, suggestively premonitory, subsided and it is felt that treatment may have averted infarction. The benefit frequently following a period of restricted activity in angina pectoris is well known. This probably occurs through increased arterial collateralization of affected areas.

That the severity and mortality of infarction are minimized when occurring at enforced rest is debatable.<sup>2</sup> An opinion may only be reached after considerable data on this subject have accumulated.

It may be asked whether complete bed rest might not, in some of these cases, slow blood flow critically in a precariously narrowed artery and precipitate thrombosis and infarction.

In our present state of knowledge, if impending infarction is suspected from the presenting symptoms, marked to complete restriction of activity is advisable, with sedation, analgesics, and vasodilators when indicated. Several weeks' rest is recommended, since it usually takes that long, according to experimental data,<sup>3</sup> for effective collateral vessels to develop. The nature of subsequent treatment will depend on existent symptoms.

Even with these measures infarction and death will be inevitable in some cases, because the speed of collateral growth will be unable to keep abreast of the circulatory losses being suffered through rapid narrowing or occlusion of an artery. Where cardiac pain does not respond to nitrites, the intravenous use of aminophylline, gr.  $7\frac{1}{2}$ , is advocated in the hope of dilating vessels supplying critical areas of the myocardium and to decrease any existing vasoconstriction. We have seen the measure dramatically relieve a patient of very severe protracted anginal pain where nitroglycerine and morphine had failed.

Papaverine, gr.  $\frac{1}{2}$  to 1 intravenously, has been suggested for treatment of the acute phase of infarction.<sup>4, 5</sup> Animals given papaverine are less prone to develop regional vasoconstriction and ventricular fibrillation following coronary ligation.<sup>6</sup> It may prove to be of value in the treatment of prolonged cardiac pain where reflex vasoconstriction might be present.<sup>5</sup>

There is experimental evidence<sup>7</sup> that the area of acute infarction and the immediate surrounding zone of impaired nutrition may serve as an irritable focus causing vasoconstriction in other parts of the myocardium through a vagal reflex. It is thought that many deaths from acute infarction may result from ventricular fibrillation beginning in these ischemic areas.

It has been suggested on the basis of animal experimentation<sup>7</sup> that atropine and aminophylline be given to prevent such a fatal outcome. Although these data are not conclusive, such therapy deserves cautious trial. The theory is that atropine will cut down the intensity of the vagal reflex. Dosage recommended is  $1/75$  of a grain intravenously every four hours. Such doses might produce harmful effects. If there is a marked increase of rate in a badly damaged heart, the precariously balanced cardiac circulation may not be able to forestall a relative ischemia, with further infarction or fatal ventricular fibrillation. In a rare case, intravenous atropine can have an opposite effect. It has produced complete A-V block with a pulse rate of 30.<sup>8</sup> A marked slowing of the heart rate may also be injurious because it may decrease the existing coronary circulation and endanger the viability of areas already poorly supplied.

#### CASE REPORTS

*Case 13.* A 70 year old ship's engineer had been perfectly well until 10 days before entry. One morning, just before starting to work, he felt a spontaneous, very strong pressure in the mid-sternal region. This lasted only five minutes. He worked as usual that day and had no discomfort. The second morning, after some customary mild exertion, he had the same feeling of mid-sternal pressure. Although less intense, it lasted 10 minutes.

Since he had the next week free, he stayed at home or took short walks. Every morning he had a 10-minute episode of moderate mid-sternal pressure. It occurred while he walked about the house, and was relieved by rest. Between attacks he felt all right.

The day before entry, he had two attacks at rest, each lasting 10 to 15 minutes. The next day, there were two bouts of pain while walking around the house. They lasted 10 and 20 minutes. At noon he walked one and one-half miles to our office. He felt well until the moment he sat down, when he had a brief, mild pain.

His heart was normal in size, sounds, and action. Blood pressure, pulse rate, temperature, leukocyte count were normal.

Since impending infarction was suspected, he was put on absolute bed rest. Electrocardiogram that day suggested a recent anterior myocardial infarct (figure 1). Sedimentation rate was 21 mm. per hour (normal, to 10 mm.).

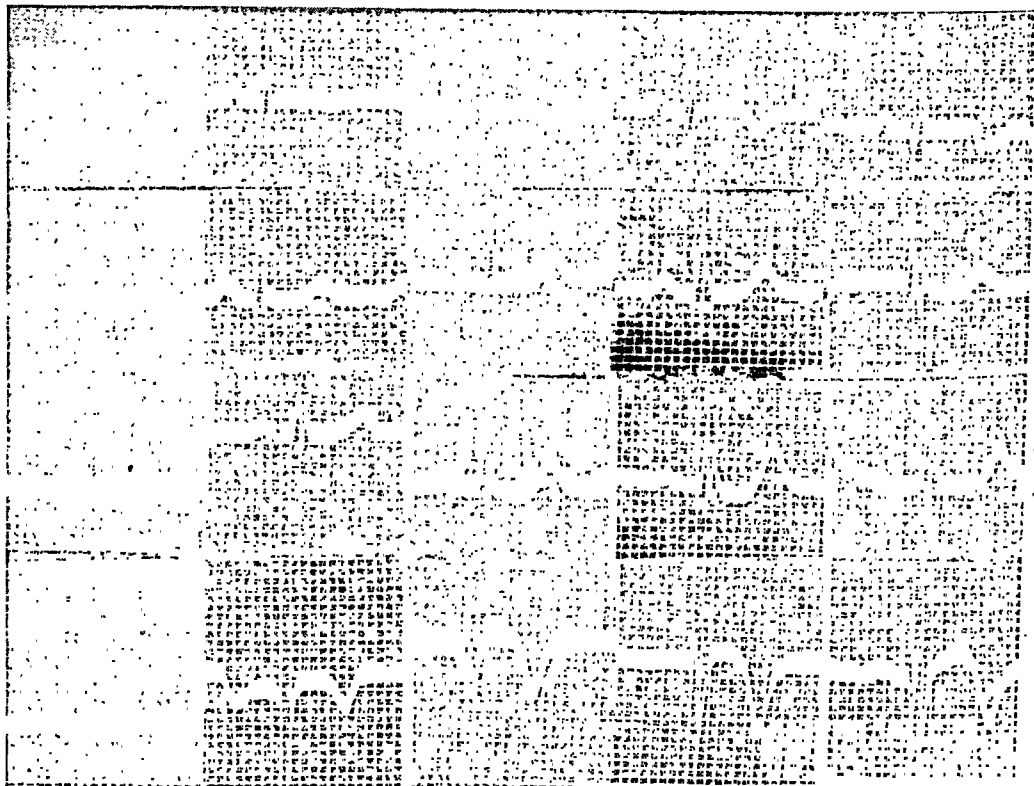


FIG. 1. Case 13: First EKG, day of entry; second EKG, sixth day of entry; third EKG, ninth day of entry, one day before second infarct; fourth EKG, thirteenth day of entry, three days after second infarct; fifth EKG, nineteenth day of entry, nine days after second infarct.

For the 10 days following hospitalization, he daily had about five mild to marked attacks of substernal pain at rest or during sleep. They lasted five to 20, rarely 30 minutes, and were very definitely and promptly relieved after taking nitroglycerine. The longer attacks occurred when the patient delayed taking nitroglycerine to see if the pain would disappear without medication. There was no fever, change in the heart sounds, blood pressure, or pulse rate. On the fifth day, electrocardiogram showed regressing T-wave changes, consistent with a healing infarct. On the eighth and ninth days he experienced several five-minute periods of interscapular aching not influenced by nitroglycerine. On the tenth day, he had two rather severe attacks of pain, one interscapular, the other substernal, for four and two hours respectively, not relieved by nitroglycerine. On the eleventh to thirteenth days he had a temperature of 37.2 to 37.6° C. Leukocyte count was 12,600. Heart, blood pressure and pulse rate remained unchanged. He was thereafter asymptomatic. Electrocardiograms showed fresh infarction.

*Case 14.* One year prior to admission, a 61 year old ship's cook began to have a mild steady ache in the left shoulder while working or after walking 50 yards. This would last five minutes and be relieved by rest.

After six months the pain became more intense on the same amount of exertion. It began to spread over the precordium and lower sternum.

In the last month, the pain appeared on even less work than usual, was even more intense, and lasted 10 to 15 minutes.

In the last week, he could hardly do much of anything without having pain. It was now accompanied by slight dyspnea. At no time were there any attacks at rest or in bed. There were no outstanding attacks.

He was obese. Heart sounds were distant; blood pressure was 140 mm. Hg systolic and 110 mm. diastolic. The first electrocardiogram indicated recent anterior myocardial infarction, with P-R interval .23-.24 sec. (figure 2). He was put to bed

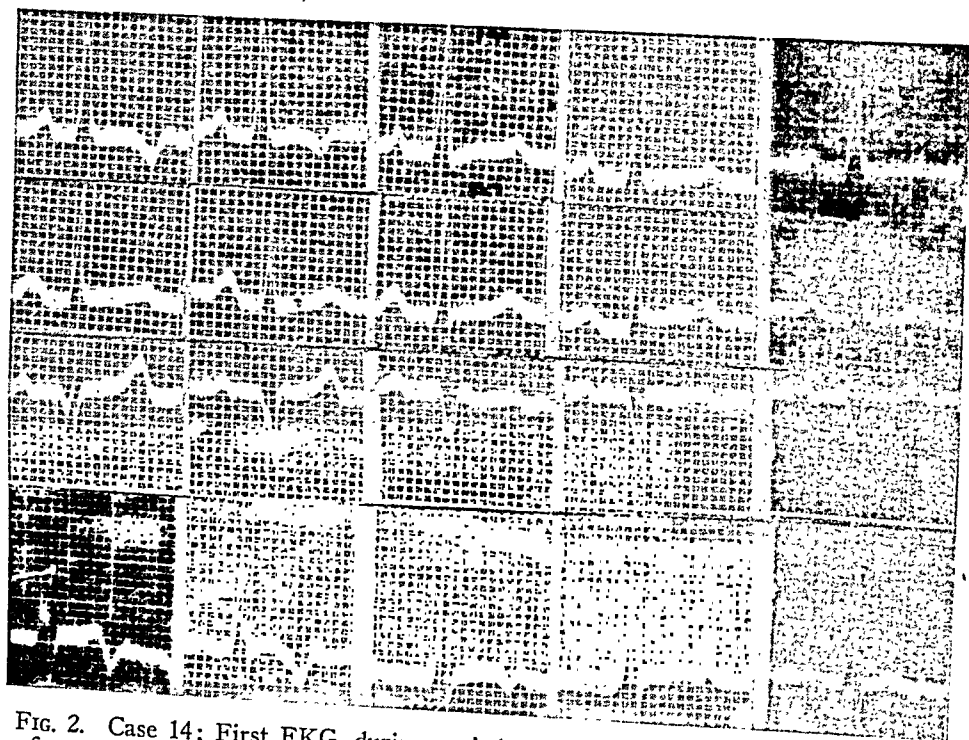


FIG. 2. Case 14: First EKG, during period of angina on exertion; second EKG, day after first spontaneous attack; third EKG, 12 days after second spontaneous attack; fourth EKG, 28 days after second attack; fifth EKG, 40 days after second attack.

with bathroom privileges, but continued to have angina pectoris if he walked about. Since we suspected impending infarction, we placed him at complete bed rest on the eighth day. On the tenth day, he had his first attack of precordial pain at rest, lasting one-half hour. On the eleventh day, electrocardiogram showed  $T_1$  less inverted, flattening of  $ST_4$ , and a decreased P-R interval of .21 sec., consistent with healing infarct. On the twelfth day, he had bilateral gnawing shoulder pain, and distress over the precordium, lasting almost an hour. These pains were not severe and no analgesics were required. Sedimentation rate increased from 13 mm. to 21 mm. during this second week. Temperature, pulse rate and leukocyte count were normal. Blood pressure gradually dropped to 118 mm. Hg systolic and 88 mm. diastolic. A third electrocardiogram showed a posterior infarction modifying the anterior pattern. The P-R interval had increased to .24 sec.

Comment: In cases of angina pectoris where attacks rapidly become more easily precipitated, existing or imminent infarction should be considered. Infarction may occur without fever, leukocytosis, or dramatic symptoms.



*Case 16.* Five and a half weeks before entry, a 59 year old ship's cook had sharp aching precordial pain lasting a few minutes. It came after running for a street car. He felt well enough to continue his work, but two nights later was awakened by a similar brief attack of pain. Two weeks before we saw him he stopped working because of sluggishness, weakness, dyspnea on exertion. At home he felt quite well until the day of entry, when he had another attack at rest similar to the others.

Examination was completely negative. Electrocardiograms showed low voltage, inverted  $T_2$  and  $T_3$  (figure 3). Since impending infarction was suspected, he was

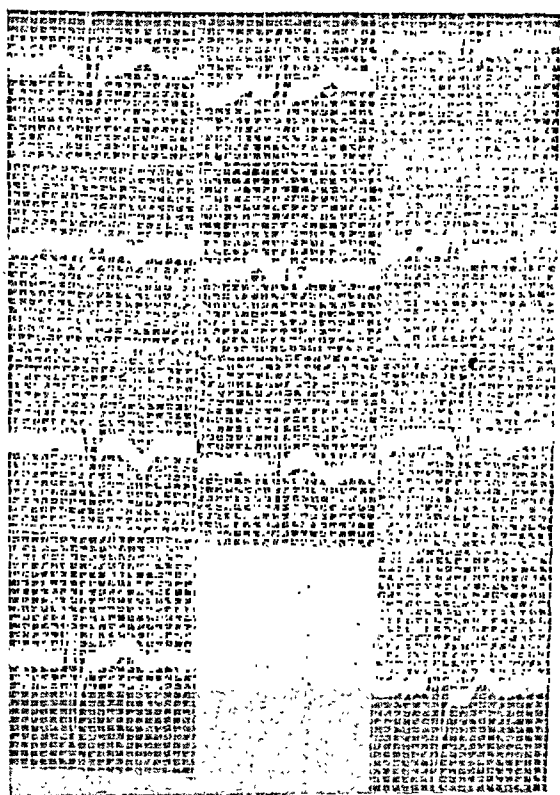


FIG. 3. Case 16: First EKG, before exercise; second EKG, after exercise until breathless, no pain; third EKG, 11 days later, following acute infarction.

observed for 10 days, ambulatory and asymptomatic. He was exercised until breathless without experiencing any pain, but there were produced electrocardiographic changes very similar to the pattern of his subsequent infarct. He was discharged and continued to rest, confined to his home. Three days later, while undressing, he suffered a very severe myocardial infarction and died in 60 hours.

*Case 4.* A 63 year old seaman first noted very mild pressure over the lower right chest brought on by exercise or a heavy meal. This continued for two years, and for the preceding three months he had increasingly marked pressure on decreasing exertion and after a large meal. It now began to be felt over the lower left chest and lower sternum also. Finally, he would have severe symptoms several times a day after any kind of exertion. Rest would bring relief, and further exertion would cause a recurrence of pain.

One week before entry, an electrocardiogram was taken and found normal. Because of the frequency and persistence of symptoms he entered the hospital.

On examination, the heart was found normal; blood pressure was 102 mm. Hg systolic and 62 mm. diastolic; leukocyte count was 8500.

On the day of entry, while sitting by his bed, he had a typical brief pain which subsided shortly after taking nitroglycerine, gr. 1/100. The next day he had a similar spontaneous pain seemingly relieved by nitroglycerine. Two days later, temperature rose to  $37.4^{\circ}$  C., and persisted for three weeks. Coupling appeared. Electrocardiograms taken after the appearance of these features showed acute changes of myocardial infarction.

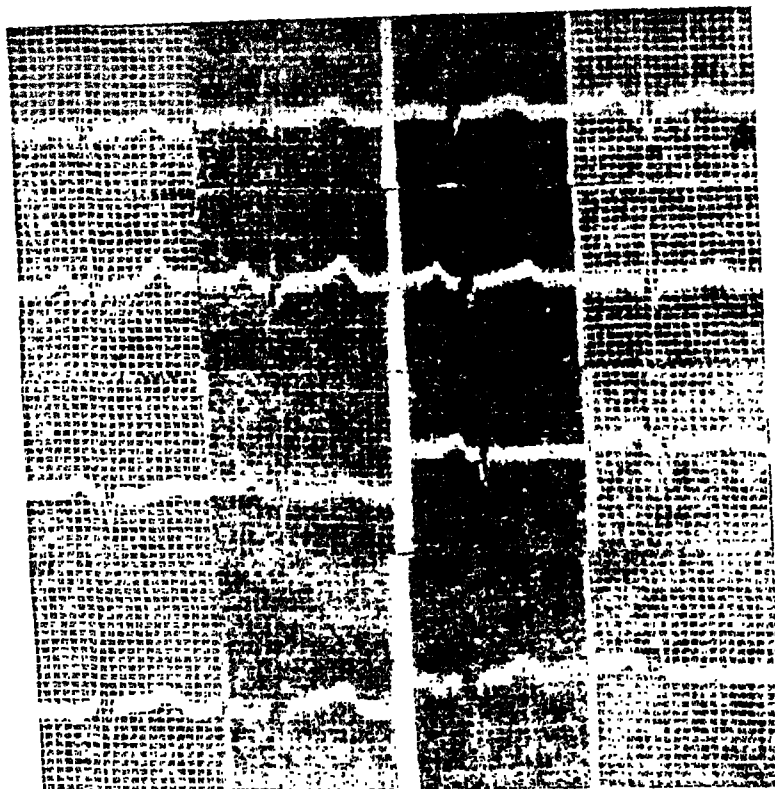


FIG. 4. Case 6: First EKG, one year before infarct; second EKG, day of infarct; after eight hours of pain; third EKG, seven days after infarct; fourth EKG, 20 days after infarct.

*Case 9.* An unusual case of preliminary pain in the right arm for seven days before acute infarction.

One week before entry, a 54 year old seaman developed a gnawing ache over the ventral surface of the right forearm and biceps. It was rather persistent and gradually became worse. A few hours before entry, while he was resting in bed, the pain became excruciating and he noted slight substernal pain.

When seen, he was weeping and beating his arm on the pillow to "knock out the pain." The next day, the chest pain became more pronounced. He developed fever, marked leukocytosis, pericarditis, ventricular tachycardia, and electrocardiographic changes of acute posterior infarction.

#### COMMENT

Acute myocardial infarction is preceded by premonitory symptoms in a goodly percentage of cases.

In a patient previously well cardiac pain, however brief and mild, sud-

denly appearing during rest or customary activity, may imply existing or imminent myocardial infarction.

In a case of preëxisting angina pectoris, cardiac pain, more readily precipitated by effort or beginning to occur at rest, may imply existing or imminent myocardial infarction.

One or more episodes of spontaneous prolonged cardiac pain may precede myocardial infarction.

In considering symptoms suspected as premonitory, it must be recognized that myocardial infarction does not inevitably follow them; but the strong possibility that it may should lead to heightened suspicion and therapeutic precautions.

#### BIBLIOGRAPHY.

1. FEIL, H.: Preliminary pain in coronary thrombosis, *Am. Jr. Med. Sci.*, 1937, cxciii, 42-48.
2. SAMPSON, J. J., and ELIASER, M., JR.: The diagnosis of impending acute coronary artery occlusion, *Am. Heart Jr.*, 1937, xiii, 675-686.
3. ECKSTEIN, R. W., GREGG, D. E., and PRITCHARD, W. H.: The magnitude and time of development of the collateral circulation in occluded femoral, carotid, and coronary arteries, *Am. Jr. Physiol.*, 1941, cxxxii, 351-361.
4. ALLEN, E. V.: Sudden occlusions of the arteries of the extremities, *Proc. Staff Meet. Mayo Clin.*, 1935, x, 678.
5. FALK, O. P. J.: The causes and prevention of sudden death in coronary disease, *Jr. Am. Med. Assoc.*, 1942, cxix, 1250-1252.
6. LINDER, E., and KATZ, L. N.: Papaverine hydrochloride and ventricular fibrillation, *Am. Jr. Physiol.*, 1941, cxxxiii, 155-160.
7. LEROY, G. V., and SNIDER, S. S.: The sudden death of patients with few symptoms of heart disease, *Jr. Am. Med. Assoc.*, 1941, cxvii, 2019-2023.
8. SALLEY, S. M.: Unusual atropine effect on ventricular tachycardia, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 456.

# A CLINICO-PATHOLOGIC STUDY OF 100 CASES OF ACUTE AND CHRONIC GALL-BLADDER DISEASE \*

By WILLIAM JOHNSON, M.D., F.A.C.S., B. E. MALSTROM, M.D., and  
BRUNO W. VOLK, M.D., *Galesburg, Illinois*

FOR the purpose of correlating the clinical manifestations and morphologic changes in gall-bladder disease, we studied the case histories of 100 patients who had been operated upon during the last 10 years.

There were 81 women and 19 men. The average age was 46.4 years. Three patients were over 70 and the youngest was a girl of 15. Table 1 shows the incidence according to age.

In 71 patients calculi were present, and in 29 the disease was non-calculous in type. Eighty-six patients were admitted during a more or less quiescent interval. Fourteen showed acute symptoms at the time of admission consisting of tenderness, a palpable mass in the right upper quadrant, fever and leukocytosis. At operation 11 of the 14 had calculi.

TABLE I  
Incidence According to Age

Age	Calculous Series		Noncalculous Series	
	Males	Females	Males	Females
10-19 yrs.		2		
20-29 yrs.		3		3
30-39 yrs.	2	15	2	4
40-49 yrs.	3	16	3	4
50-59 yrs.	3	16	4	6
60-69 yrs.	2	7		2
70-80 yrs.		2		1

*Etiology.* Gall-bladder disease is essentially a chronic disease. Although acute cholecystitis does occur, most of the so-called acute cases are either recurrent or acute exacerbations of infection in a chronically diseased gall-bladder which has caused trouble for some time.

Infection may reach the gall-bladder through various routes. It may ascend from the duodenum by way of the papilla of Vater. Following influenza and pneumonia the infection may enter the gall-bladder through the hepatic route, whereas the portal route may carry infection after typhoid fever and colon bacilli infection. When an inflamed colon or duodenum is in direct contact with the gall-bladder the infection may enter by direct extension, and the infection may spread from the liver or the pancreas by way of the lymph stream.

\* Received for publication April 3, 1943.

From the Department of Surgery and Pathology, Cottage Hospital, Galesburg, Illinois.

Pregnancy is an etiologic factor because of the interference with the normal emptying of the gall-bladder. It has been shown in animal experiments that only when the uterus is empty will the gall-bladder respond to the administration of fat. Although none of our patients was pregnant at the time of admission, 45 of the calculous series and 18 of the non-calculous gave a history of one or more pregnancies.

Typhoid fever as an etiologic factor is becoming less common. A history of typhoid fever was elicited in only two patients and in none of the cases was it possible to recover typhoid bacilli from the bile.

*Symptoms.* The difference between the symptoms of the two types of gall-bladder disease is only one of degree and not of kind. The cholecystitis is the essential condition. The calculi are only incidental and aggravate an existing inflammation, but in themselves are not capable of producing cholecystitis, as inflammation is due to infection with microorganisms. The longer the cholecystitis has been present, the more likely it is to be complicated by calculi. McEvedy found that calculi are absent in 20 per cent of patients with definite cholecystitis. McCarty, in studying 21,523 cases at the Mayo Clinic, found that only 65 per cent of the surgically removed gall-bladders contained stones. In our 86 patients with chronic gall-bladder disease, calculi were present in 60.

Analyzing the symptoms present in this group of 86 cases we find distention, flatulence, belching, nausea and vomiting, loss of weight, fever in a negligible percentage of the chronic cases, jaundice, and the vague complaints of indigestion, discomfort in the epigastrium, and sour taste. Table 2 shows the distribution of these symptoms in the calculous and non-calculous cases.

TABLE II  
Relative Incidence of Signs and Symptoms in 86 Cases of Chronic Calculous and Noncalculous Cholecystitis  
(60 patients had concrements; 26 had stoneless gall-bladders)

Symptoms	Calculous Series		Noncalculous Series	
	No.	Per Cent	No.	Per Cent
Distention and belching ..	20	33.33	19	73.07
Constipation .....	14	23.33	17	26.92
Vomiting and nausea .....	45	75.00	10	38.46
Colics .....	40	66.66	10	38.46
Jaundice .....	19	31.66	4	15.38
Typical symptoms of gall-bladder disease .....	45	75.00	12	46.15
Vague symptoms of abdominal distress .....	5	8.33	7	26.92

*Cholecystography.* In our experience cholecystography shows accurate diagnosis in well over 90 per cent of the cases. Graham and Cole state that cholecystography is merely a method of studying the functional activity of the gall-bladder rather than a means of indicating the exact pathologic lesions

present. It does not give the final diagnosis and is only to be considered as a contributory aid for the diagnosis of gall-bladder disease. The symptoms are more reliable than the roentgenologic report of a pathologic gall-bladder. The cholecystographic findings in relation to the pathologic lesions found at operation are frequently disappointing. In most of the cases in which visualization showed a delayed function or a faint shadow of the gall-bladder the cystic duct was patent and the gall-bladder contained bile. Occasionally the existence of diabetes mellitus, penetrating duodenal ulcer, or simple spastic conditions of the gastrointestinal tract may produce false results of the Graham-Cole test. Surgical exploration should be advised in cases in which the clinical history of gall-bladder disease is questionable even though the visualization tests suggest a normal function.

Forty-one cases of our series of chronic cholecystitis studied by cholecystography showed a poor or nonfunctioning gall-bladder, and of these 33 were distinctly pathologic at operation, three were slightly so, and two showed indefinite changes. On the other hand, three cases showed negative results of the visualization test but definite disease at operation, such as thickening and scarring of the gall-bladder wall with or without pericholecystic adhesions.

The error of the cholecystographic diagnosis was greatest in the cases with either faint shadow or delayed function without stones, whereas the Graham-Cole test proved correct in those cases in which there was a faint shadow or no visualization of the gall-bladder with distinct evidence of calculi.

*Pathology.* Pathologists are not in entire agreement as to what is a normal gall-bladder. It is estimated that 30 to 50 per cent of all adults over 30 years of age have chronic cholecystitis in one form or another. It is a well known fact, confirmed at autopsy, that many patients with definite disease of the gall-bladder never had symptoms. The normal gall-bladder shows lymphocytic infiltration. Lymphoid follicles in the submucosa may be numerous and are commonly found.

TABLE III  
Relation of Cholecystographic Results to Pathologic Findings in Gall-Bladders  
Operated on as Chronic Cholecystitis

Cholecystographic Findings	Definite Lesions		Indefinite Lesions		Normal Gall-Bladders	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Poor or nonfunctioning gall-bladders.....	33	80.48	3	7.32	2	4.88
Normal functioning gall-bladders.....	3	7.32				

In our series, 47 chronically diseased gall-bladders were removed at operation and examined histologically; 25 contained stones and 11 were free from calculi. In both varieties we could distinguish three types of gall-

bladders: (a) those which showed signs of clinical activity; (b) those removed during the quiescent intervals, and (c) those removed because of vague symptoms of pain in the upper abdomen and indigestion over a long period of time. In these cases there was a certain asymmetry of the pathologic process. In a considerable number we observed a patchy distribution of the inflamed areas. Inflammatory changes were usually more advanced in the region of the fundus and in the body of the gall-bladder; they were more pronounced in the areas adjacent to the liver than in the free portions of the wall, which seems to confirm the theory of spreading of the infection by direct continuity from the liver.

True ulcers of the gall-bladder are very rare, and we found only three in our series, all occurring in the acute cases with calculi.

The histologic examination of the chronically diseased gall-bladders proved that the microscopic changes are very seldom an accurate index of the severity of the symptoms. Gall-bladders which were supposed to be responsible for the most aggravating symptoms of cholecystitis showed almost no change at microscopic examination. Lymphocytic infiltration is no criterion of chronic cholecystitis; small round cells may be present in the normal gall-bladder wall even in childhood. They may be found as small solitary lymph follicles or they may be diffusely distributed throughout the wall, especially in the submucosa, probably as a part of a general lymphatic hyperplasia.

The thickening of the gall-bladder wall may be extreme in one degree; in one of our specimens the wall was 1.5 cm. thick. In some cases the thickening is due to fibrosis; the connective tissue replaces the muscular and elastic tissues and the resulting scar tissue converts the gall-bladder into an inert sac containing an extremely contracted cavity. In the majority of our cases, however, the gross specimen appeared markedly thickened, whereas on section the mucosa and muscularis appeared quite normal. The thickening was due to a marked edema of the subserosa. In some of our specimens fat was collected in the subserous and muscular layers, a factor which also contributed to the apparent extreme thickening of the gall-bladder wall.

Of the 12 cases which on gross examination had marked thickening of the wall, only one showed fibrosis of all coats of the gall-bladder, the other 11 exhibiting marked edema in the subserosa. All the specimens contained calculi, usually large solitary stones. We rarely found a considerable number of smaller concretions in that type of gall-bladder disease. Sometimes a gall-bladder contracted markedly after fixation simulating a gross thickening of its wall, a feature which was clarified at histologic examination.

The epithelium of the gall-bladders, as a rule, showed no change. As Boyd points out, it is remarkable how intact the surface epithelium is even in the worst looking gall-bladders. Only in the three specimens where ulcers were found could desquamation and destruction of large areas of epithelium be observed.

Five of the examined gall-bladders had a normal mucosa and showed no marked evidence of inflammatory reaction.

With the exception of some chronically diseased gall-bladders which showed an edematous and markedly swollen wall with dense lymphocytic infiltration, abundant formation of granulation tissue and thickened swollen villi, in the subacute or quiescent cases, the remaining 35 specimens were divided into two groups: (a) those with slight lymphocytic infiltration where a small number of lymphocytes was scattered throughout the mucosa and partly through the inner layers of the muscular coat, and (b) those cases with marked diffuse or focal small round cell infiltration throughout the wall. The infiltrating cells were lymphocytes, plasma cells and cells of wandering mononuclear type.

Fourteen cases were only slightly infiltrated with lymphocytes, whereas 21 exhibited marked small round cell infiltration. The calculous as well as the noncalculous variety were almost equally distributed in either group, a fact which again proved that stones are not essential in the production of cholecystitis but that their presence may only be an aggravating factor in the existing inflammation.

Rokitansky-Aschoff sinuses were observed in a high percentage of our cases. The hernia-like outpouchings of the mucosa frequently passed through all coats of the wall, here and there forming small dilated bags in the subserosa or in the serosa. Since they were found in the normal as well as the diseased gall-bladders, they certainly do not indicate the severity of the cholecystitis. We observed, however, that the Rokitansky-Aschoff sinuses were rather shallow in all cases where the muscular coat was hypertrophic.

In nearly all the specimens the submucosa showed an increase of the connective tissue and the walls were only slightly infiltrated by small round cells, even where the subepithelial mucosa was densely infiltrated by lymphocytes.

The muscularis and subserosa showed considerable change and were also involved in the cases in which the mucosa apparently was quite normal. The muscular coat rarely takes an important part in the thickening of the gall-bladder wall. We found hypertrophy of the muscularis in four cases, two of the calculous type and two of the noncalculous variety, which suggests that hypertrophy of the muscularis is not necessarily associated with the presence of stones. In our cases, the hypertrophy of the muscular coat was manifested by an increase in the size and to a certain degree in the amount of the smooth muscle cells. As a rule, the thickening of the muscularis was more prominent in the mid-portion of the gall-bladder than on both ends.

Edema, though never as outspoken as in the serosa, was found in seven of our chronic cases, showing a slight spreading of the smooth muscle fibers and commonly exhibiting a diffuse infiltration of small round cells. The edema of the muscular coat when present always was associated with an extensive edema of the subserosa which is one of the outstanding features of the chronically inflamed, thickened gall-bladders, as observed in all specimens which at gross examination revealed a marked thickening of the wall. Except for edema, the characteristic lesions in the subserosa were dilated capil-



laries and lymphatics, areas of hemorrhage, and focal collection or diffuse infiltration of chronic inflammatory cells. In our five cases with much involvement of the serosa, two were of the noncalculous and three of the calculous variety.

Five cases of hydrops were found, all with stones. The histologic examination showed a rather thin wall. The mucosa was intact but atrophied, showing only a small number of short sessile villi. The muscular as well as the sub-serous coat revealed a high degree of atrophy, and the wall was diffusely infiltrated by a relatively small number of chronic inflammatory cells and fibroblasts. The contents were sterile.

If a pyogenic infection is superimposed, empyema of the gall-bladder may develop, a complication we found in four cases of the calculous type. Histologically, there was thickening, especially of the muscular and subserous coats. The mucosa contained gangrenous patches with sloughing off of varying sized areas. The wall was diffusely infiltrated by numerous inflammatory cells and showed hyperemia as well as dilatation of the lymphatics and pronounced edema of the subserosa. In one case the vascular supply was damaged, producing thrombosis of the arteries of the submucosa followed by necrosis and gangrene of the mucosa.

Cultures were sterile in two of the four empyemata. In a third case we found staphylococci and *B. coli* in comparatively small numbers.

Seven of our histologically examined gall-bladders were acutely inflamed and of the calculous variety. The inflammation probably was due to an acute obstruction of the cystic duct. The characteristic features were edema especially in the outer coat and diffuse infiltration of the wall with lymphocytes and polymorphonuclear leukocytes which were most marked in the muscularis and subserosa. Compared to acute inflammation of the appendix, it is remarkable that the gall-bladder is infiltrated by a relatively small number of polymorphonuclear leukocytes and that the lymphoid elements showing diffuse or focal infiltration in some of our cases were the predominant inflammatory cells. The gall-bladder wall showed distended blood vessels and lymphatics as well as patches of recent hemorrhage. In one specimen there were multiple small abscesses in the wall. The surface epithelium showed large areas of desquamation.

The pathologically acutely inflamed gall-bladder is not always identical with the clinically acute cholecystitis. Not infrequently after the subsidence of fever, leukocytosis, pain and tenderness, the gall-bladder removed at operation may show evidence of acute inflammation. On the other hand, the histologic feature of recovery of acute cholecystitis is the appearance of eosinophiles in the gall-bladder wall, as we found in two cases. The clinical symptoms in these cases had subsided 10 days before operation. Besides the finding of eosinophiles the microscopic examination revealed the signs of chronic inflammation and repair, thus confirming the clinical symptoms.

The appearance of lipoid in the gall-bladder has created widespread discussion. Mentzer showed that cholesterosis is present in 37 per cent of

gall-bladders seen at necropsy and in 22 per cent of surgical specimens. In our series we found 10 lipoid gall-bladders, seven of the calculous and three of the noncalculous variety. The lipoid deposit, which is an ester of cholesterol, in most cases is confined to the epithelial cells in the tips of the villi of the mucosa of the gall-bladder, lying for the most part at the base of the cells. In two of our gall-bladders it was scattered throughout the stroma. The lipoid in the gall-bladder, as a rule, is of no practical importance, although it may be the first stage of an aseptic process which can eventually set free concretions of cholesterolin, thus forming a nucleus for further deposits. Although it is often an additional finding in chronic cholecystitis, it is likewise found in normal specimens. Aschoff and Boyd found it as frequently in the normal as in the diseased gall-bladder.

Gall-bladder disease is quite often associated with involvement of the liver. In our series the liver was affected in eight of the calculous cases and one of the noncalculous, the involvement varying from a thickening of the capsule to enlargement, mottling of the liver and abscess formation.

The pancreas may be affected by direct extension as well as by the haematogenous or lymphatic route. In our series the pancreas showed enlargement and diffuse fibrosis in five cases. In none of the cases showing involvement of the liver or pancreas was a microscopic examination of the diseased organs done.

The appendix was removed in 37 cases at the time of cholecystectomy. The inflammatory changes in 32 appendices examined microscopically are to be considered as coincidental, as many of them were either definitely normal or showed approximately the same percentage of chronically diseased appendices as found on microscopic examination of appendices studied at autopsy.

Pericholecystic adhesions were present in 39 cases, 24 calculous and 15 noncalculous. They varied from slight adhesions of the fundus to the duodenum to extensive fibrous adhesions involving the whole gall-bladder as well. They apparently had no bearing on the preoperative symptoms as quite a number of patients who complained of severe and frequent biliary attacks showed none or just a few adhesions at operation. The post-operative course also revealed no connection with the presence or extent of the pericholecystic adhesions.

Table 4 shows additional operative findings in the 86 cases.

*Final Results.* Follow-up reports were received from 72 patients, 65 with chronic cholecystitis and seven with acute inflammation. The period of observation following discharge from the hospital varied from five months to nine years.

\* Of the 65 patients with chronic cholecystitis, 35 of the 45 who had stones were either permanently cured or greatly improved, four had only temporary complete relief, and six showed no improvement at all. Of the 20 patients in the noncalculous group, 13 reported permanent relief, three had only temporary complete relief, and four were made worse by the operation.

TABLE IV

Additional Operative Findings of Chronic Calculous and Noncalculous Cholecystitis  
(60 patients had concrements, 26 stoneless gall-bladders)

Findings	Calculous Series		Noncalculous Series	
	No.	Per Cent	No.	Per Cent
Pericholecystic adhesions.....	24	40.00	15	57.69
Hepatitis.....	8	13.33	1	3.84
Pancreatitis.....	5	8.33	—	—
Enlarged portal glands.....	5	8.33	3	11.52
Appendix				
Normal.....	5	8.33	2	7.68
Acute inflammation.....	1	1.66	—	—
Chronic inflammation.....	17	28.33	—	—

In both groups the ones showing only temporary relief reported recurrence of symptoms from three months to one year after cholecystectomy.

The seven patients with acute cholecystitis from whom final reports were received were either completely cured or greatly improved.

Regardless of how long the patient had had symptoms, roughly 75 per cent obtained good results from cholecystectomy and approximately 25 per cent were no better after operation than before.

From histologic examination of the gall-bladder in the cases with good postoperative results, it appears that the removal of the gall-bladders which presented definite pathologic changes was followed by better clinical results than cholecystectomy in cases which showed only minimal pathologic changes in the gall-bladder.

Table 5 shows the final results in this series of 100 cases.

TABLE V

Postoperative Results According to Follow-Up Reports

Results	Calculous Series				Noncalculous Series			
	Acute		Chronic		Acute		Chronic	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Cured.....	4	36.36	30	50.00	1	33.33	8	30.76
Improved.....	2	18.18	5	8.33	—	—	5	19.23
Temporarily improved..	—	—	4	6.66	—	—	3	11.53
Unimproved or worse...	—	—	6	10.00	—	—	4	15.38
No reply.....	5	—	15	—	2	—	6	—
Total.....	11		60		3		26	

### CONCLUSIONS

From this study it would appear that noncalculous cholecystitis is best handled by medical means. When this management does not adequately relieve the patient cholecystectomy is recommended.

In the calculous type surgery is the treatment of choice.

Improvement in the results of treatment of gall-bladder disease requires a better knowledge and understanding of the physiology of the gall-bladder and biliary tract than we possess at this time.

#### BIBLIOGRAPHY

- ANDREWS, EDMUND: Pathologic cases of diseased gall-bladder: I. A new classification, *Arch. Surg.*, 1935, xxxi, 767-793.
- ASCHOFF, G.: Lectures on pathology, 1924, Paul B. Hoeber, Inc., New York.
- BABLOCK, A. A.: Statistical study of 888 cases of biliary tract disease, *Bull. Johns Hopkins Hosp.*, 1924, xxxv, 391-409.
- BEHREND, ALBERT, and GRAY, HOWARD K.: Acute cholecystitis: problems created by an attempt to correlate its clinical, surgical and pathological manifestations, *Surgery*, 1938, iii, 195-199.
- BOYD, WM.: Surgical pathology, Third Edition, 1933, W. B. Saunders Company, Philadelphia.
- BROWN, M. J.: Noncalculous chronic gall-bladder disease, *Clin. Jr. Surg.*, 1938, xli, 238-254.
- EISS, STANLEY, and WHALEY, J. H.: Changes in the biliary system after cholecystectomy. The causes of recurrence of gall-bladder symptoms, *Am. Jr. Surg.*, 1935, c, 921-926.
- FEINBLATT, H. M.: The influence of primary infection in gall-bladder disease, *New England Jr. Med.*, 1928, cxc, 1973.
- FERGUSON, A. N., and PALMER, W. L.: Cholecystography, its clinical evaluation; a study of 2070 cases, *Jr. Am. Med. Assoc.*, 1933, c, 809-812.
- GRAHAM, E. A., and COLE, W. H.: Roentgenologic examination of the gall-bladder, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 613.
- HAUSER, H.: Practical application of cholecystography, *Radiology*, 1933, xxi, 427-477.
- JUDD, E. S., and PRIESTLY, J. T.: Ultimate results from operations on the biliary tract, *Jr. Am. Med. Assoc.*, 1932, xcix, 887-891.
- KUNARTH, CARL A.: The stoneless gall-bladder. An analysis of one hundred cases treated by cholecystectomy, *Jr. Am. Med. Assoc.*, 1937, cix, 183-187.
- MCCARTY, W. C.: The gall-bladder and its disease, *Proc. Staff Meet. Mayo Clin.*, 1936, xi, 805.
- McEVEDY, P. J.: Gallstones and cholecystitis, *Clin. Jr.*, 1935, lxiv, 111-115.
- MACKEY, W. A.: Cholecystitis without stones. Investigation of 264 operated cases from the clinical, radiological and pathological aspects, *Brit. Jr. Surg.*, 1939, xxii, 274-295.
- MENTZER, S. H.: The status of gall-bladder surgery based on a study of 14,000 specimens, *Jr. Am. Med. Assoc.*, 1928, xc, 607-610.
- NICKEL, A. L., and JUDD, E. S.: Cholecystitis: a bacteriologic study of 300 surgically resected gall-bladders, *Surg., Gynec., and Obst.*, 1936, I, 655.
- PETERSON, T.: Gall-bladder disease: a clinical study, *Minnesota Med.*, 1935, xviii, 123-127.
- ROSE, L. B.: Some problems and results in cholecystography, *Radiology*, 1934, xxii, 197-201.
- WEISS, SAMUEL: Pre-operative and postoperative medical management of biliary conditions, *Med. Rec.*, 1939, ci, 311-316.

# SUBCLINICAL VITAMIN DEFICIENCY

## V. THE ASSAY OF SUBCLINICAL THIAMIN DEFICIENCY \*

By MILDRED CARLEEN HULSE, M.A., NORMAN WEISSMAN, PH.D.,  
ELMER STOTZ, PH.D., MARSHALL CLINTON, M.D., JOSEPH W.  
FERREBEE, M.D., *Boston, Massachusetts*

### INTRODUCTION

THE assay of subclinical thiamin deficiency is primarily a problem in defining changes in thiamin nutrition before signs or symptoms of deficiency make their appearance. Accomplishment of this end presupposes a knowledge of normal thiamin nutrition; that is, normal extracellular and intracellular thiamin concentrations, and the size and sequence of variation in these values which may precede the occurrence of clinical deficiency.<sup>1</sup> The purpose of the present study is to determine whether measurable changes in either extracellular or intracellular thiamin concentrations occur in subclinical thiamin deficiency. For comparison, observations are also reported on thiamin excretion and on pyruvate metabolism.

### METHOD

Six normal male medical students, 20 to 25 years of age, were placed on a thiamin deficient diet of 2700 to 3300 calories (2000 non-fat) containing, by calculation and by analysis, less than 0.2 milligram of thiamin. Supplements of vitamins A, D, C, riboflavin, and niacin were supplied daily and, in addition, four of the subjects were given gelatin capsules and told that the capsules would contain either lactose or thiamin.

A gauge to changes in cellular thiamin concentrations was obtained by measuring the yeast stimulating activity of samples of skeletal muscle removed from the gluteal region with the Silverman biopsy needle.<sup>1, 2</sup> Samples were removed fasting in the early morning. The yeast fermentation method of thiamin assay<sup>2</sup> was used without correction for sulfite blanks.<sup>3</sup> The estimates of thiamin concentration, therefore, exceed the true values<sup>4</sup> and are useful chiefly in showing the decrease that occurs during subclinical deficiency. Estimation of changes in extracellular thiamin concentration was obtained in a similar manner by following the yeast stimulating activity of samples of fasting blood plasma.<sup>5</sup>

\* Received for publication September 20, 1943.

From the Laboratory of Dental Medicine, Harvard School of Dental Medicine; the Medical Clinic, Peter Bent Brigham Hospital, and the Biochemical Laboratory of the McLean Hospital, Boston, Massachusetts.

Aided by grants from the Williams and Waterman Fund, Research Corporation, New York City, and the Nutrition Foundation, New York City.

This report is a preliminary study whose completion has been delayed by other work related to the war effort.

Since muscle thiamin is predominantly intracellular, its concentration was expressed in terms of another predominantly intracellular constituent, namely phosphorus, rather than in terms of wet weight of muscle.<sup>4</sup> The thiamin concentrations so expressed are relatively independent of possible variations in the proportion of extracellular and intracellular phase obtained in the small muscle biopsies. Muscle phosphorus was determined in each biopsy sample by the Kuttner-Lichtenstein technic<sup>6</sup> of phosphorus estimation.\*

The urinary excretion of thiamin was determined by the thiochrome method.<sup>7</sup> Tolerance tests for the estimation of thiamin deficiency by measurement of thiamin excretion were performed according to the procedure of Robinson, et al.<sup>8</sup>

Blood pyruvate concentrations<sup>9</sup> were measured fasting, before, immediately after, and on recovery from a standardized exercise,<sup>10</sup> and before and after the ingestion of 50 grams of glucose.<sup>11</sup> Blood lactate concentrations were determined on the same samples.<sup>12</sup> Air samples were analyzed in duplicate for carbon dioxide and oxygen content on a Haldane-Henderson gas analyser. The exercise used was a 10 minute walk on a 3 mile an hour treadmill with an 8 degree slope.

General clinical condition was estimated from routine inquiry and observation and from the daily measurement of weight. Four of the subjects were allowed to continue their usual school work. Two were asked to increase their physical activity and for this purpose walked 15 to 20 miles a day.

The experiments were performed in late fall and early winter and the following observations were made.

## RESULTS

The subjects complained of the monotony of their diet almost from the first day; they did not, however, lose appetite and left to their own wishes managed in all but one instance to eat enough to maintain weight. The subject, Ki, who walked 15 to 20 miles each day over a period of 18 days, lost 3 kilos, chiefly in the last portion of this period.

During the first week of thiamin deprivation neither the subjects nor the examiners were able to convince themselves that symptoms of deficiency were making their appearance. Minor fluctuations in sense of well-being were distinguished but were of short duration and erratic occurrence. In contrast, during the latter part of the second week each of the four subjects continuing to that time felt and looked dispirited, whether from monotony of diet or other cause they could not say. On the fifteenth and sixteenth days of the deficient régime two of the subjects, Ki and Ko, received 2 milligrams of thiamin in their daily lactose "placebo" capsule. Since they were unaware of this addition, it is significant that each experienced within about 18 hours a definite improvement in sense of well-being.

\* We are indebted to Miss Virginia Rowland for the phosphorus analyses and to Miss Marion Brian for her preparation and supervision of the diets.

As has been previously observed,<sup>13, 14, 15</sup> the urinary excretion of thiamin decreased promptly when the subjects were placed upon the deficient diet. Instead of normal values of the order of 100 micrograms per 24 hours, values of the order of 25 to 50 micrograms were observed at the end of a few days of thiamin deprivation. The excretion of thiamin at the end of two weeks' deficiency was less in subject Ki who exercised than in subject Ko who did not; 23 micrograms per 24 hours for Ki, compared to 47 micrograms for Ko.<sup>16</sup> Tolerance tests at the end of two weeks' deficiency showed that in subjects F and L, 6 and 8 per cent respectively of the 5 milligrams of thiamin administered with the noon meal was excreted in 24 hours. The lower limit of normal chosen by Robinson et al. for this test was an excretion of 7 per cent.<sup>8</sup>

TABLE I

Effect of Thiamin Deficient Diet upon Yeast Stimulating Activity of Plasma of Normal Men  
(Values expressed in thiamin equivalents, millimicrograms per milliliter of plasma)

Subject	Control Value	Deficient Diet		Normal Diet	Remarks
		7 days	18 days	4 days	
Ko	6.0	—	3.9	4.8	Usual exercise
Ki	4.9	—	2.9	4.5	Walked 15-20 miles a day
S	6.1	4.1	—	—	Usual exercise
B	5.4	2.5	—	—	Walked 15-20 miles a day

The observations on plasma are given in table 1. The yeast stimulating activity of plasma decreased on the deficient diet and returned toward normal with the resumption of a normal diet. The decrease in plasma activity was more marked in the patients who exercised.

TABLE II

Effect of Thiamin Deficient Diet upon Yeast Stimulating Activity of Skeletal Muscle  
(Values expressed in thiamin equivalents, micrograms per milligram of muscle phosphorus)

Subject	Normal Control	After 18 Days of Deficient Diet	Remarks
L	.41	.29	Usual exercise
F	.35	.28	Restricted exercise
Ko	.43	.28	Usual exercise
Ki	.37	.27	Walked 15-20 miles a day
S	.48	—	Usual exercise
B	.32	—	Walked 15-20 miles a day

The observations on muscle are given in table 2. The higher control values were observed in the individuals who had the higher plasma values, Ko and S. There is evidence that the differences in control values reflected differences in recent intake of thiamin.<sup>17</sup> Subject S, who had the highest value, 0.48, had eaten a quantity of chicken and nuts at midnight, eight

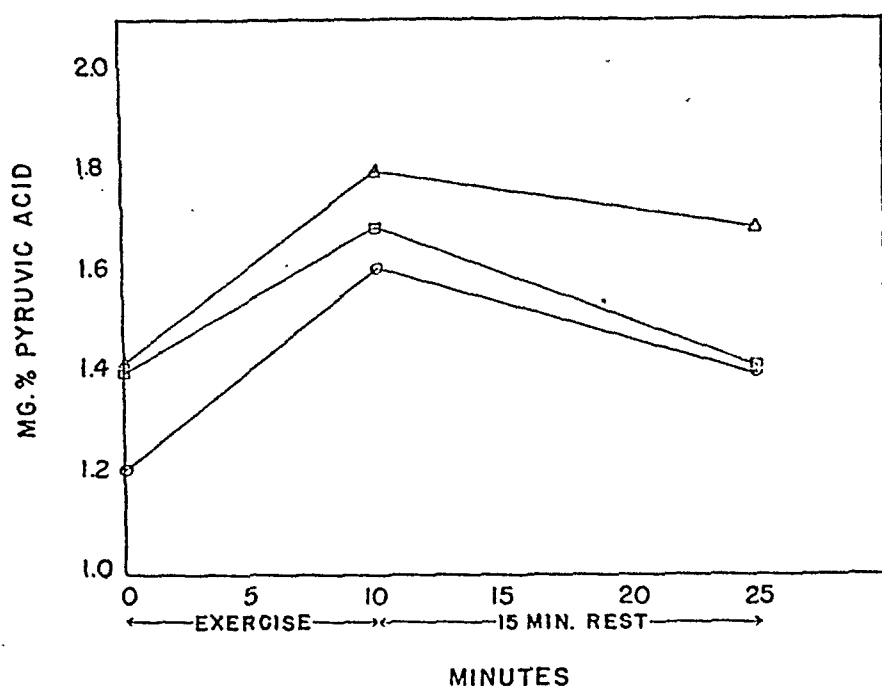


FIG. 1. Changes in milligrams per cent of pyruvic acid in blood of subject Ko, immediately after, and 15 minutes after 10 minute exercise.

○ = Normal control  
 □ = After 7 days on deficient diet  
 △ = After 18 days on deficient diet

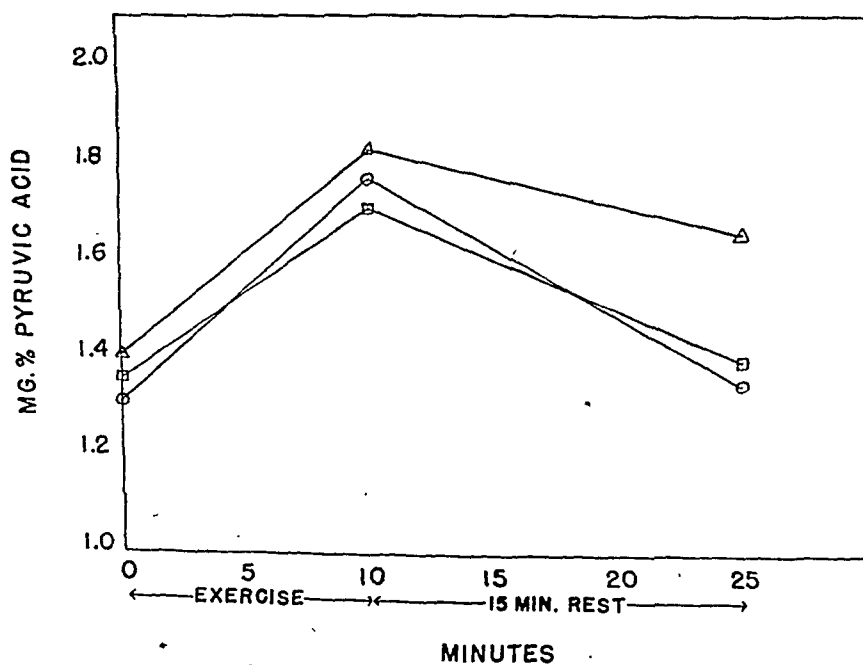


FIG. 2. Changes in milligrams per cent of pyruvic acid in blood of subject Ki, immediately after, and 15 minutes after 10 minute exercise.

○ = Normal control  
 □ = After 7 days on deficient diet  
 △ = After 18 days on deficient diet



hours before the control biopsy was taken. After 18 days of deficient diet a common level of  $0.28 \pm 0.01$  was reached, quite independent of the control values or of the amount of exercise performed.

The observations on blood pyruvate are given for patients Ko and Ki in figures 1 and 2. After 18 days of deficient diet there was a delay in the return of blood pyruvate concentrations to normal following exercise. Similar delay was not observed after stimulation by glucose administration in subjects F and L.

In both subjects Ko and Ki there is definitely a slower decrease in blood pyruvate after the exercise period, which may indicate a decreased ability to metabolize the pyruvate. However, since absolute blood pyruvate values are dependent on several factors which are difficult to control, it has been suggested that the ratio of blood pyruvate to lactate would be of more critical value in assessing an impaired pyruvate metabolism.<sup>12</sup> Such ratios did not show any conclusive changes during the thiamin deficiency period.

Thiamin deficiency of 18 days' duration did not produce changes in oxygen consumption during exercise or changes in the daily excretion of citric acid.<sup>18, 19, 20 \*</sup>

## DISCUSSION

In the present experiments, clinical evidence of thiamin deficiency was detectable by the end of the second week of thiamin deprivation. The symptoms observed were vague, being chiefly a change in sense of well-being that could be improved by thiamin administration. As in the experience of Williams, et al.<sup>13</sup> the symptoms were sufficient for recognition in a carefully controlled group of experimental subjects, but it is doubtful whether they could have been distinguished and correctly interpreted in a single individual presenting himself for medical examination. It seems fair, therefore, to apply the term "subclinical" to the 18 day period of thiamin deficiency used in these experiments, and to discuss as "subclinical" the abnormalities of thiamin nutrition observed by means of the laboratory assays.

The abnormalities observed were as follows: a decrease in the yeast stimulating activity of samples of plasma, a decrease in the urinary excretion of thiamin, a decrease in the yeast stimulating activity of samples of skeletal muscle, and an impaired ability to metabolize pyruvate. Assuming for the moment that the decrease in the yeast stimulating activity of plasma and muscle represents losses of thiamin from these tissues,<sup>4, 5</sup> the observations may be interpreted as indicating that during thiamin deprivation there occurs a decrease in the concentration of thiamin circulating in the extracellular fluid, a consequent diminution of the renal excretion of thiamin, an eventual decrease in cellular thiamin concentrations, and a resultant impairment of pyruvate metabolism. All these changes occur to a measurable degree in the

\* We are indebted to Dr. Martin L. Deakins of the Laboratory of Dental Medicine for the citric acid analyses.

period of deprivation termed "subclinical." The selection of any one of them for measurement as a criterion diagnostic of subclinical deficiency is, therefore, a matter of choice to be decided on such basis as: convenience, or availability of laboratory technic; discriminative capacity, in the sense of sensitivity to small changes in nutritional status; and specificity, or freedom from involvement in irrelevant physiologic or pathologic variables.

In general, there is reason for feeling that measurements of thiamin excretion reflect changes in the concentration of freely diffusible extracellular thiamin<sup>5</sup> and that measurements of blood pyruvate reflect changes in the concentration of fixed enzymatically active, intracellular thiamin.<sup>21</sup> The assay technics are, therefore, to a certain extent interchangeable. But since renal function also affects thiamin excretion,<sup>22</sup> and since variations in carbohydrate metabolism and pyruvate formation also affect blood pyruvate concentration, it is evident that the indirect assays of thiamin nutrition, namely thiamin excretion and blood pyruvate concentration, are applicable primarily to essentially normal individuals in whom normal baselines of renal function and pyruvate formation may be assumed. The direct assays of extracellular or intracellular thiamin concentration, that is, plasma and muscle analyses, on the other hand, should have a wider applicability once further experience has established their normal ranges and interrelationships.

#### SUMMARY

Subclinical thiamin deficiency was induced in six normal young men by thiamin deprivation of seven to 18 days' duration.

Clinical symptoms were minimal and not in themselves sufficient for diagnosis.

Measurable changes, however, were observed in the yeast stimulating activity of samples of fasting plasma, in the urinary excretion of thiamin, in the yeast stimulating activity of samples of skeletal muscle, and in the metabolism of pyruvate.

The probable significance of these measurements and their use in the diagnosis of subclinical thiamin deficiency are discussed.

#### CONCLUSION

A measurable decrease in both extracellular and intracellular thiamin concentrations may be detected in subclinical thiamin deficiency.

#### BIBLIOGRAPHY

1. HULSE, M. C., WEISSMAN, N., OWEN, P. S., and FERREBEE, J. W.: Subclinical vitamin deficiency, *Science*, 1943, xcvi, 47.
2. ATKIN, L., SCHULTZ, A. S., and FREY, C. N.: Ultramicrodetermination of thiamin by the fermentation method, *Jr. Biol. Chem.*, 1939, cxxix, 471.
3. SCHULTZ, A. S., ATKIN, L., FREY, C. N., and WILLIAMS, R. R.: Application of the sulfite cleavage of thiamin to the yeast fermentation method, *Jr. Am. Chem. Soc.*, 1941, lxiii, 632.

4. HULSE, M. C., WEISSMAN, N., ROWLAND, V., GROSS, R., and FERREBEE, J. W.: Subclinical vitamin deficiency. VI. Thiamine in skeletal muscle of infants and children, *Am. Jr. Dis. Child.*, 1944, lxxvii, 30.
5. HULSE, M. C., WEISSMAN, N., and FERREBEE, J. W.: Subclinical vitamin deficiency. IV. Plasma thiamin, *Jr. Clin. Invest.*, 1944, xxiii, 297.
6. KUTTNER, T., and LICHTENSTEIN, L.: Micro colorimetric studies, II, *Jr. Biol. Chem.*, 1930, lxxxvi, 671.
7. FERREBEE, J. W., and CARDEN, G. A.: A procedure for the routine determination of vitamin B<sub>1</sub> in urine, *Jr. Lab. and Clin. Med.*, 1940, xxv, 1320.
8. ROBINSON, W. D., MELNICK, D., and FIELD, H., JR.: Urinary excretion of thiamin in clinical cases and the value of such analyses in the diagnosis of thiamin deficiency, *Jr. Clin. Invest.*, 1940, xix, 399.
9. BUEHING, E., and WORTIS, H.: The stabilization and determination of pyruvic acid in the blood, *Jr. Biol. Chem.*, 1940, cxxxiii, 585.
10. LU, G. D., and PLATT, B. S.: The metabolism of pyruvic acid in normal and vitamin B<sub>1</sub>-deficient states. V. The effect of exercise on blood pyruvate in vitamin B<sub>1</sub> deficiency in man, *Biochem. Jr.*, 1939, xxxiii, 1538.
11. BUEHING, E., STEIN, M. H., and WORTIS, H.: Blood pyruvate curves following glucose ingestion in normal and thiamin-deficient subjects, *Jr. Biol. Chem.*, 1941, cxi, 697.
12. STOTZ, E., and BESSEY, O. A.: The blood lactate-pyruvate relation and its use in experimental thiamin deficiency in pigeons, *Jr. Biol. Chem.*, 1942, cxliii, 625.
13. WILLIAMS, R. D., MASON, H. L., WILDER, R. M., and SMITH, B. F.: Observations on induced thiamine (vitamin B<sub>1</sub>) deficiency in man, *Arch. Int. Med.*, 1940, lxvi, 785.
14. FERREBEE, J. W., WEISSMAN, N., PARKER, D., and OWEN, P. S.: Tissue thiamin concentrations and urinary thiamin excretion, *Jr. Clin. Invest.*, 1942, xxi, 401.
15. WILLIAMS, R. D., MASON, H. L., and WILDER, R. M.: The minimum daily requirements of thiamine of man, *Jr. Nutr.*, 1943, xxv, 71.
16. JOHNSON, R. E., DARLING, R. C., FORBES, W. H., BROUHA, L., EGAÑA, E., and GRAYBIEL, A.: The effects of a diet deficient in part of the vitamin B complex upon men doing manual labor, *Jr. Nutr.*, 1942, xxiv, 585.
17. FERREBEE, J. W., WEISSMAN, N., PARKER, D., and OWEN, P. S.: The thiamin content of human tissue, *Res. Pub. Assoc. Nerv. and Ment. Dis.*, 1943, xxii, 42.
18. PUCHER, G. W., SHERMAN, C. C., and VICKERY, H. B.: A method to determine small amounts of citric acid in biological material, *Jr. Biol. Chem.*, 1936, cxiii, 235.
19. SOBER, H. A., LIPTON, M. A., and ELVEHJEM, C. A.: The relation of thiamine to citric acid metabolism, *Jr. Biol. Chem.*, 1940, cxxxiv, 605.
20. KREBS, H. A.: The biochemical lesion in vitamin-B<sub>1</sub> deficiency, *Chem. and Ind.*, 1938, lvii, 213.
21. EVANS, E. A., JR.: The biochemical action of the vitamins, 1942, The University of Chicago Press, Chicago.
22. NAJJAR, V. A., and HOLT, L. E., JR.: Studies in thiamin excretion, *Bull. Johns Hopkins Hosp.*, 1940, lxxvii, 107.

## HEMOPTYSIS IN TUBERCULOSIS, WITH A DIFFERENTIAL DISCUSSION OF OTHER CAUSES \*

By LEWIS J. MOORMAN, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

IF romancing were permissible in medicine, we might indulge in an interesting consideration of the sharp turns hemoptysis has wrought in the lives of important personages and in the history of the world. It often precipitates a psychological panic through the fear of impending dissolution and, then, spurns death in order to condition destiny. Allen K. Krause once said, "Sometimes a man will write a new kind of history. Its keynote will be the shaping of human destiny by disease." In such a history, hemoptysis should have a prominent place.

Hippocrates' statement that "the spitting of pus follows the spitting of blood, consumption follows the spitting of this and death follows consumption" is in line with the prevailing early belief that hemoptysis was a causative factor in tuberculosis, rather than an effect; a belief apparently not seriously questioned until the time of Richard Morton in the seventeenth century. Though Morton was doubtful as to whether hemoptysis caused tuberculosis, he advised that every patient spitting blood should be diagnosed as having consumption and that treatment should be instituted at once. In the beginning of the nineteenth century, Bayle definitely concludes that "phthisis provoked the hemoptysis, but not that it is the result of it." Andral, Louis and Villemin concurred in this conclusion. Even after Bayle, Laennec and Louis, through their clinical and pathological investigations, had greatly clarified the picture of tuberculosis and freed hemoptysis from this unjust charge, there was a temporary reversion toward the old belief that hemoptysis figured as a cause of tuberculosis, rather than an effect.

In our own day, we have witnessed a tendency on the part of many doctors to accept the spitting of blood as being virtually pathognomonic of tuberculosis, with a consequent neglect of differential diagnosis. In the light of present knowledge, such presumption is inexcusable. This is the more surprising since Aretaeus and other Greek physicians recognized many causes of blood spitting 1,800 years ago.

Considering the psychological effects of hemoptysis, Aretaeus wrote, "frightful despair sometimes seizes such persons; for really, who is there who can have a bringing up of blood without having a terrible fear of death." Although this is true, the well-poised patient may meet the issue of blood with calm fortitude and accept the shaping of destiny with resignation.

The correlation of bedside and autopsy findings, the invention of the stethoscope and the microscope, the discovery of the tubercle bacillus, the development of the roentgenogram, bronchography, bronchoscopy and col-

\* Presented before a Regional Meeting of the American College of Physicians, Kansas City, Missouri, May 8, 1943.

lapse therapy have brought a better understanding of hemoptysis, its causes and its control.

Literally, hemoptysis means spitting of blood, but clinically, it means the expectoration of blood which comes from the larynx, the trachea, the bronchi, or the lungs. After struggling with the Greek description of such bleeding, Francis Adams considered "a bringing up" as the most literal English translation. When called to see a patient with blood spitting, the first duty of the physician is to distinguish between true hemoptysis and blood which comes from the nose, mouth, or pharynx. Time will not permit the enumeration of all the possible pathological conditions above the larynx, which may give rise to so-called spurious hemoptysis. The differential diagnosis is not always easy, and occasionally all efforts fail, at least temporarily, even with the aid of a skilled nose and throat specialist. This is particularly true when the spitting of blood is intermittent and the examining physician has only the history to guide him. Such cases should be required to report for examination during the period of blood spitting. Not infrequently blood in the throat is due to post nasal oozing, bleeding gums, or varicose veins at the base of the tongue. Patients who awaken after a night's sleep with blood in the throat, which is expectorated without cough, may have slight bleeding from the gums, or nasopharynx. Patients who give a history of slight blood spitting during the day, with no obvious cause, should be examined for varicosities, at the base of the tongue. Often, in such cases, bleeding can be induced through friction caused by voluntary muscular contraction and movement of the tongue. If, after a thorough investigation, doubt exists, a careful search for tubercle bacilli is indicated and the diagnosis should await definite pathognomonic data. These simple sources of blood spitting, located above the larynx, are stressed because they frequently cause unwarranted fear of pulmonary disease and because they may exist in patients who are at the same time suffering from manifest pulmonary tuberculosis. In either case, they may give rise to great alarm and a prompt diagnosis with positive reassurance may quickly lift the anxious victim out of a depleting psychological slump.

Before discussing true hemoptysis, malingering must be mentioned. Self-induced traumatic hemoptysis is rare in civilian practice, but among the less scrupulous inmates of impregnable prisons, it is not uncommon. Such culprits have designs upon hospitalization where escape may be less difficult. Now that we are at war it is important to remember that unstable or unscrupulous soldiers may seek the shield of chronic invalidism and government compensation, as preferable to the responsibilities of war with its inevitable hazards. Among the common methods employed are forceful gum sucking, cutting the gums or soft palate with a razor blade and traumatizing the posterior nares or the pharynx with a needle or some other sharp instrument. Constant awareness and vigilance on the part of physicians and nurses should discover the cause.

True hemoptysis is a common symptom of pulmonary tuberculosis, oc-

currence in approximately 50 per cent of all cases at some time during the course of the disease, and it may be said that in spite of increasing knowledge of other sources, tuberculosis continues to be the most common cause of this shocking symptom. It may be one of the earliest manifestations of tuberculosis, and in that event it often proves to be a genuine boon to the patient because it puts the fear of God in his heart and drives him to his physician in a receptive mood. It is more common and likely to be more profuse as the disease advances, especially in the ulcerative types. The hemorrhage may be slight, representing capillary oozing; moderately severe from eroded blood vessels; or profuse from the rupture of aneurysmal vessels into tuberculous cavities. It is the latter type which occasionally leads to sudden death. There may be a great gush of blood from the mouth, a few last gasps for breath and the exsanguinated patient lies limp and wan in his own blood when the doctor arrives. This picture may be simulated by the rupture of an aneurysm of the aorta or one of its branches, into a bronchus. If the patient lives until the doctor arrives, the prognosis is sufficiently good to justify the reassurance which is so essential in the treatment of hemoptysis. Patients may recover from profuse pulmonary hemorrhage and never bleed again, or the hemorrhage may recur from time to time with ultimate recovery or a fatal termination. Slight and moderate bleeding is more common, less dangerous and psychologically, not so shocking.

In the great majority of cases, the application of modern diagnostic methods leads to a definite diagnosis. Yet, with the mounting number of doubtful cases, augmented by what apparently represents increasing frequency of non-tuberculous broncho-pulmonary conditions, prompt differential diagnosis becomes imperative. Although it is important to make an early diagnosis when pulmonary tuberculosis is the cause, it is even more important in the acute pneumonias, bronchogenic carcinoma, lung abscess and bronchiectasis, all of which are common sources of hemoptysis. The truth of this statement becomes clear when we consider the brilliant results of early modern medical and surgical therapy in these conditions and the utter failure which may follow delay. When hemoptysis occurs in the course of manifest pulmonary tuberculosis under management, usually its source is easily determined; but when it occurs in a person not previously examined, a thorough diagnostic study is required. If pulmonary tuberculosis is found to be present, this is to be accepted as the most probable cause of the blood spitting. It must be remembered that hemoptysis may arise from tuberculous ulceration of the bronchi or trachea. As a rule, such lesions are associated with manifest pulmonary tuberculosis and, usually, acid fast bacilli are found in the sputum, even though active pulmonary tuberculosis is not demonstrable.

As a rule, the differentiation between tuberculosis and other causes of true hemoptysis is not difficult, but it must be remembered that, occasionally, tuberculosis may cause blood spitting when the disease is not definitely demonstrable, either by physical examination, or roentgenogram. Tubercle

bacilli have been found in the sputum of patients in whom physical examination and roentgenographic studies were reported as negative. In such cases, the history and the symptoms of toxemia, linked with a diligent search for acid fast bacilli, may make the diagnosis reasonably certain.

Recently Jackson and Diamond,<sup>1</sup> after careful diagnostic studies, reported 436 non-tuberculous cases with hemoptysis as follows: Bronchiectasis, 138; primary carcinoma of bronchus, 82; tracheobronchitis, 74; pulmonary abscess, 51; no evidence of disease, 34; non-suppurative pneumonitis, 15; suppurative pneumonitis, 11; adenoma of bronchus, 11; secondary cancer of lung, 6; lobar atelectasis, 4; primary carcinoma of trachea, 2; suppurating pneumoconiotic lymph node discharging into bronchus, 1; non-specific granuloma of bronchus, 1; streptothricosis, 1; chondroma of bronchus, 1; osteoma of trachea, 1; dermoid cyst communicating with bronchus, 1; broncholithiasis, 1; neurofibroma involving wall of bronchus, 1. Among the causes not mentioned by Jackson and Diamond<sup>1</sup> are: mitral stenosis; blood dyscrasias; trauma, with or without rib fracture; exploratory needling; pneumonia; infarction of the lung, embolic or thrombotic; bubonic plague; bronchial fluke; blast injuries; sporotrichosis; hydatid cyst; fat embolism; cystic disease of the lung; aortic aneurysm; foreign body; arteriosclerosis of the pulmonary vessels; trichinosis and possibly strenuous physical effort and severe coughing, as in whooping cough; also, vicarious hemorrhage from interrupted menstruation has been listed as a cause.

These figures give a very good idea of the non-tuberculous sources of hemoptysis and the Jackson and Diamond series indicates the relative frequency of the more important causes. Apparently, bronchiectasis, bronchogenic carcinoma and lung abscess are more common than they used to be, but no doubt improved diagnostic methods and increased alertness on the part of the physician, account for the seeming increase in frequency. At any rate, the diagnostic problem becomes more acute and differential diagnosis more obligatory.

Unfortunately, the bronchopulmonary conditions which figure as the common causes of hemoptysis may so closely simulate tuberculosis and each other that diagnosis becomes most difficult, yet the skilled clinician knows that each of these conditions has its own distinctive clinical pattern with which he is quite familiar and from which it seldom wholly strays. If pulmonary tuberculosis is closely simulated by bronchiectasis, bronchogenic carcinoma, pulmonary abscess or tracheobronchitis, a careful comprehensive study of the history usually reveals a clue which at least temporarily classifies the condition for further diagnostic investigation. Such a tentative diagnosis serves as a guide for physical exploration and determines the judicious employment of such diagnostic procedures as successive roentgenographic films guided by fluoroscopy and supplemented by bronchography when indicated. Laboratory studies of sputum, blood examinations and finally bronchoscopic explorations, biopsies and the examination of exudates may help to clarify the diagnosis.

Bronchiectasis is the most common non-tuberculous source of hemoptysis. Without going into great detail, the following features are to be emphasized as important in the differential diagnosis: a progressive, productive cough following an acute bronchopulmonary episode, usually dating back to childhood; purulent sputum, occasionally foul smelling and persistently negative to all tests for acid fast bacilli; cough and expectoration precipitated or aggravated by lying down, stooping over or laughing; and finally, clubbing of the fingers.

Of course, all stages of bronchiectasis must be considered and those cases which are clinically less obvious and the cases of dry bronchiectasis may add to the diagnostic difficulties. The physical examination, with roentgenographic examination, bronchography and bronchoscopy as indicated to supplement the history, should lead to a definite diagnosis.

Hemoptysis from bronchogenic carcinoma should be considered when persistent, productive cough with blood streaking or frank hemorrhage develops without obvious acute bronchopulmonary episodes. The probability of carcinoma is enhanced if the cough becomes progressively worse and resists all therapeutic measures. Additional evidence may or may not be elicited by physical examination. The reduction or suppression of breath sounds on the affected side is a significant sign. Roentgenographic studies may be equally uncertain, especially in early bronchogenic carcinoma. In every case of hemoptysis unexplained after a careful diagnostic study a bronchoscopic examination should be advised and pieces of tissue secured for histological studies when possible. This is particularly true when the above symptoms dominate the history. When gross pathological changes appear it may be too late. Unfortunately, pneumonectomy is seldom feasible after hemoptysis occurs. In other words, spitting of blood is not an early sign of bronchogenic carcinoma.

Often, hemoptysis from pulmonary abscess may be diagnosed by a carefully taken history and roentgenographic studies. If there is a history of a provocative episode such as an operation about the nose, throat or mouth, bronchopneumonia or the aspiration of a foreign body followed by fever and cough, the diagnosis becomes reasonably certain. The cough may be unproductive for a few days, then gradually or suddenly give rise to purulent sputum, often foul smelling, with an unpleasant sweetish taste. If the roentgenogram shows evidence of pneumonitis with cavity formation and the sputum is persistently negative for acid fast bacilli, the diagnosis of pulmonary abscess is assured. In some cases it may be necessary to secure different roentgenographic exposures or even the employment of the Bucky technic in order to demonstrate the abscess cavity. If doubt remains bronchoscopy should be employed.

Because of the war, hemoptysis caused by rupture of the fragile lung tissue from blast either in the air or under water must be considered. The history of exposure to such an injury with associated effects upon other organs should aid in the diagnosis.



Considering our far-flung battle fronts, bronchial fluke as a cause of hemoptysis also must have consideration. It is said that casualties from the Pacific presenting puzzling blood spitting have been observed in San Francisco Hospitals and that, after some delay, it was found that the hemoptysis was due to bronchial fluke apparently acquired from pickled crab meat captured from the Japanese. After some delay, the eggs of the fluke were found in the sputum, thus confirming the diagnosis.

Hemoptysis with the rather characteristic history of tracheobronchitis in the absence of physical signs and roentgenographic evidence of disease should strongly suggest this condition. If the symptoms are persistent, bronchoscopic examination should be employed for diagnostic and therapeutic purposes.

The many less frequent causes of hemoptysis are to be considered after the above have been ruled out by exhaustive diagnostic studies and the further differential diagnosis must depend upon the process of elimination. In 40 years of private practice Ware<sup>2</sup> observed 386 cases of hemoptysis. In his interesting report it appears that 68 of the cases were followed from two to 37 years without subsequent symptoms of pulmonary disease. It must be remembered that these cases were reported in 1860 and did not come under the sharp scrutiny of modern methods. Blood spitting which can not be explained after searching diagnostic examinations, including all roentgenographic and laboratory studies and bronchoscopy, demands continued observation and repeated examinations until a diagnosis is arrived at or a definite interval of safety has passed.

The emergency treatment of hemoptysis presents a fertile field for the ancient art of medicine. Very few patients escape serious psychological conflicts when they witness the issue of blood from their own throats. Immediately, they anticipate death, advancing disease or both. If emotionally unstable, they are panic stricken; if well poised, they may be no less concerned, but through cultivated inhibitions they may conceal serious psychological conflicts. Since sedation is the most important immediate therapeutic indication, it is wise to remember that psychological sedation through artful reassurance is much safer than soporific sedation which deadens the cough reflex and endangers the patient's future. Judicious, authoritative command of the agitated patient and the distraught relatives prepares the way for scientific management according to individual needs. Often the above plan must be supplemented by mild sedative medication. The hypodermic use of codein or morphine in small doses may be indicated. In many cases bromides or barbiturates by mouth may be sufficient. If the psychological approach has been successful, cough and physical agitation may be brought under voluntary control, thus limiting the questionable employment of the more powerful sedatives. In obstinate cases, however, morphine may prove to be the splint necessary to temporarily control the break. We must admit that laudanum was the friend of nearly all the old time "lungers" who did not have the benefit of modern therapy.

After securing the maximum mental and physical rest, other therapeutic considerations arise. We may dismiss all the medicinal agents designed to increase the coagulation of the blood by the admission that aside from their psychological effects, they are virtually useless unless blood tests demonstrate a definite need for them.

Absolute rest in bed is essential. If hemorrhage is profuse and the expectoration of blood is not satisfactory, a favorable posture for drainage should be sought. This is doubly important if sedatives have impaired the cough reflex. Mechanical measures have assumed a position of increasing importance, both in the emergency and in the treatment of continuous or recurrent hemoptysis. Time will not permit a detailed account of these measures, but attention is called to the fact that they range from simple procedures to restrict pulmonary expansion and undue respiratory agitation when the patient is seized with paroxysms of coughing, to collapse therapy which includes artificial pneumothorax, phrenic nerve interruption, thoracoplasty, lobectomy and pneumonectomy.

Long before the author was fully apprised of the importance of mechanical influences in the control of hemoptysis, a ranchman was admitted to the Farm Sanatorium because of recurrent profuse pulmonary hemorrhages. The history indicated that when it seemed that death might conclude the initial attack, two of the boys on the ranch tied a rope around his chest as they would tie the lariat of a bucking broncho around a snubbing post. Apparently strapping the thorax down tightly controlled an attack which occurred while he was in the Sanatorium. Since then, the author has often employed strapping or a tight bandage over the lower half of the thorax and the abdomen with good mechanical and psychological effect. When all the less radical procedures fail or if the emergency is too urgent for such deliberate therapy, artificial pneumothorax should be given a trial. As a rule, with the aid of the patient, who often has a definite sense of location, the clinician can determine which side is bleeding. If this is impossible and roentgenographic studies are not feasible or available the best possible guess should be considered a sufficient guide for the institution of pneumothorax. Usually such a guess is adequate for control, provided adhesions do not render collapse impossible or unsatisfactory. It is possible the altered intrathoracic pressure may exercise a favorable influence even though bleeding is not coming from the collapsed lung. Recently in an emergency, the author after hurried auscultation of the chest, collapsed the left lung for the control of alarming recurrent hemoptysis. He was guided by extensive bubbling râles over the left lung. Though the bleeding was promptly controlled, later diagnostic studies, including roentgenograms, suggested the right lung as the most probable source of bleeding. On two occasions simultaneous bilateral pneumothorax has been considered necessary to control persistent dangerous hemorrhage.

If artificial pneumothorax is not successful, phrenic nerve interruption should be considered. The successful use of pneumoperitoneum combined

with interruption of the phrenic nerve has been reported. When all other methods fail, thoracoplasty may be considered for the control of recurrent hemoptysis. In neoplasms, bronchiectasis, and occasionally in lung abscess and cystic disease, lobectomy or pneumonectomy may be indicated.

#### SUMMARY

Brief consideration has been given to the development of our knowledge of hemoptysis; the various sources of hemoptysis and the relative importance of the principal causes; the differential diagnosis; the treatment, in which reassurance and other psychological measures are stressed as being more important than promiscuous dosing with sedatives and coagulants; and finally, mechanical agencies which in some cases are life saving.

#### BIBLIOGRAPHY

1. JACKSON, C. L., and DIAMOND, S.: Haemorrhage from the trachea, bronchi and lungs of nontuberculous origin, *Am. Rev. Tuberc.*, 1942, xlv, 126.
2. WARE, JOHN: Haemoptysis as a symptom, Publications of The Massachusetts Medical Society, 1860.

# DIRECT MEASUREMENTS OF THE EFFECTS OF BROMIDES, SODIUM AMYTAL AND OF CAFFEINE IN MAN \*

By EDMUND JACOBSON, PH.D., M.D., F.A.C.P., *Chicago, Illinois*

MANY publications appear each year concerning the influence of stimulants and sedatives in animals and in man. Investigations have afforded much indirect evidence of the action of such agents on the nervous and muscular systems. However, direct quantitative measurements of functional states in the intact organism following the administration of pharmacological substances have never been attempted, doubtless because of lack of suitable instruments. The possibility of such investigation has finally been opened by advances in electrophysiology in the last decade. Most convenient for the present investigation, which I believe marks a first step in this special field, is apparatus capable of registering the average microvoltage, yielding values which can be plotted against time, as recently described.<sup>1</sup> Comparison of the data secured under controlled conditions, before and after such administration, can lead to knowledge of considerable practical as well as scientific importance.

Since no method has been developed to estimate the activity of the intact nervous system as a whole at any instant, we continue to be limited to sampling methods applied to a particular section of the organism. For approximately one half century, the prevailing custom among those who wished to test the functional condition of the nervous system was to determine the excitability of the knee-jerk and other deep reflexes during the resting state.<sup>2</sup> An alternative procedure would be to measure action-potentials against time in the quadriceps femoris muscle, as reported recently.<sup>3</sup> Likewise, variations in contraction in the flexors of the forearm can be conveniently studied under controlled conditions, when the arm is supported in a position of rest.<sup>4</sup> In line with the traditional view deriving as above mentioned, the results of recordings on more than 300 individuals during the last decade seem to justify the belief that the electrical state of the right arm flexor muscles can afford a sample of considerable value toward indicating the functional state of the organism at any instant and, therefore, can serve as a therapeutic test. That the effects of motor stimulants and sedatives are registrable in neuromuscular responses is not surprising, for this must evidently be possible if they act upon motor centers, anterior horn cells, peripheral nerves or on muscles directly; but even if they act directly only on higher centers in the brain, a consequent increased or decreased response there will determine increase or decrease of efferent discharge as a secondary but inevitable effect.

\* Received for publication October 13, 1943.

From the Laboratory for Clinical Physiology, Chicago.

Read in abstract before the Section of Pharmacology at the Boston Meeting of The Federation of American Societies for Experimental Biology, April 4, 1942.

The present investigation concerns the influence of bromides, sodium amytal and caffeine on man, as far as can be determined in terms of action-potentials.\* Many contributions have followed the invention of concentric electrodes suitable for recording potentials from single fiber groups by Adrian and Bronk.<sup>5</sup> However, as stated previously: "In seeking a quantitative indication of tonus in a muscle as a whole, we are led away from the employment of micro-electrodes and of concentric electrodes, which were found suitable in the investigation of the electrical activity of single fibers or of small groups of fibers discharging as a unit. If it were possible to place a pair of concentric electrodes in juxtaposition with each and every muscle fiber in the muscle group tested and so to measure each and every discharge, a plot of voltages and frequencies against time for all the fibers would be an ideal electrical measurement of contraction in the muscle group. Since this is beyond possibility, wire electrodes are inserted into the muscle tissue where an indefinite number of fibers discharge variously from instant to instant. Obviously, at any instant the p.d. in the electrodes is the resultant from discharges in the surrounding muscles mass."<sup>3</sup> Accordingly the method presently employed depends upon the number of motor units in action and the frequency of discharge in each motor unit.

As one of the many antecedents to the present study, it was necessary to determine whether lesser grades of contraction, including what is commonly called "tonus," are likewise marked by correspondingly smaller electrical changes. For this purpose, apparatus capable of yielding measurements of transient voltages lower than had previously been employed in medicine and in most departments of physics was accordingly developed. It was found that the slightest degrees and variations of muscular contraction, including tonus, could be electrically measured, even in the intact animal, if the voltage sensitivity was sufficiently high.

When the string galvanometer is employed, as in electrocardiography, but with special amplifier equipment, the photographed deflection of the string can be made as great as one centimeter per microvolt—which is about one thousandfold the magnification seen in heart records. Obviously, when amplification of such high order is used, it is necessary in each study to make control tests in which suitable resistances ("inanimate objects") replace the living tissues under investigation. Such control tests afford values which must be allowed for in order to arrive at final quantitative determinations.

Measurement of photographed string deflections occurring at various rates per second involved great labor when a technician had to examine each line individually with the aid of a magnifying glass. Accordingly, newer equipment was devised whereby much of the labor of measurement is performed in the instrument itself. With the Integrating Myovoltmeter (or Neurovoltmeter), as the new instrument is called, action-potentials (within certain limits) are measured without photography. The instrument includes

\* Ampules of sodium amytal were kindly furnished by Eli Lilly & Company; caffeine by Abbott & Company.

an amplifier of standard type, with a characteristic fairly flat for frequencies from 20 to 10,000. The amplified potentials are rectified and averaged over each two minute period during the test. These averaged values can be plotted against time, representing the results of the test. To standardize the instrument, 1 microvolt a.c. at 57 cycles is applied across the input terminals of the amplifier and readings are made on the galvanometer dial for two minute periods. From the mean of several such readings is subtracted the mean determined from the same number of readings made through the same circuits under identical conditions except that no current passed through the standardizer. The mean value thus determined per microvolt per two minute interval is divided by 2, in order that all results in the present investigation can be stated in terms of microvolts d.c.

At any instant the total rectified output is indicated by the position of a needle on the dial of a microammeter. Fluctuations of this needle enable the investigator visually to follow the variations in contraction in the muscle studied; if the subject extends his leg, the needle moves up on the dial accordingly and stays up as long as the extension is maintained; but if the muscle becomes limp and relaxed, the needle turns toward zero.

Since the potentials to be considered demonstrably occur upon muscular contraction, whether during movement or the maintenance of a steady state, I shall hereinafter use the term "integrated action-potentials" for what are customarily called "action-currents" or "action-potentials."

Electrodes consisted of platinum iridium wires about 11 mm. long and 0.011 inch in diameter inserted perpendicularly into the tissues. As a rule these were inserted crosswise in the right biceps-brachial muscles about two inches above the apex of the angle formed by the skin when the forearm is bent to about 90°. They were about 2½ inches apart and were equidistant from the volar midline. This location minimizes the electrocardiogram which tends to appear when electrodes are located lengthwise in these muscles.

Fifteen subjects were employed without advance information as to the purpose of the study. They were adults of both sexes actively engaged in business pursuits of various kinds\* and were as a rule in fair health, as found upon examining them physically. Although some were of nervous disposition, as a group they seemed fairly representative of average or "normal" individuals. Every effort was made to prevent them from learning the nature of the medicine administered. This effort appeared to be successful except in one or two instances, when the color of the triple bromide solution betrayed its character to the subject who was familiar with it.

During the tests the subject lay in a semi-soundproof room. Conversation was not permitted. The instruction was to lie quietly with eyes closed. A few minutes were permitted for him to "settle down" in each instance, before recording was initiated. Previous experience with similar tests without medication suggested that a 30 minute period of recording would prob-

\* There were three tailors, three waiters, two office girls, two vault clerks, one elevator operator, one plumber, one mailman, one medical secretary and one clerical manager.

TABLE I

The values represent contraction-voltages for each subject with and without medication (averaged for three periods following each type of medication or for three corresponding control tests).

Subject	Sex	Age	Without Bromides	With Bromides	Sodium Amytal	Sterile Water	Caffeine
1	F	22	1.58	1.02	.73	1.12	1.26
2	F	21	.49	.38	.27	.34	.35
3	M	47	2.04	1.05	.67	3.54	4.76
4	M	54	.67	.18	.21	.24	.84
5	F	34	.20	.26	.08	.76	.86
6	M	26	.24	.22	.26	.25	.56
7	M	42	.56	.37	.34	.23	1.03
8	M	40	3.21	2.44	1.02	1.85	2.02
9	F	31	2.65	1.66	.68	1.42	2.90
10	M	44	.39	.53	.42	.31	.67
11	M	42	.70	1.04	.61	.38	.95
12	M	51	.28	.21	.33	.38	1.04
13	M	44	.49	.59	.19	.54	.46
14	M	63	1.61	.42	.24	.28	.38
15	M	43	1.33	.42	.31	.83	1.83

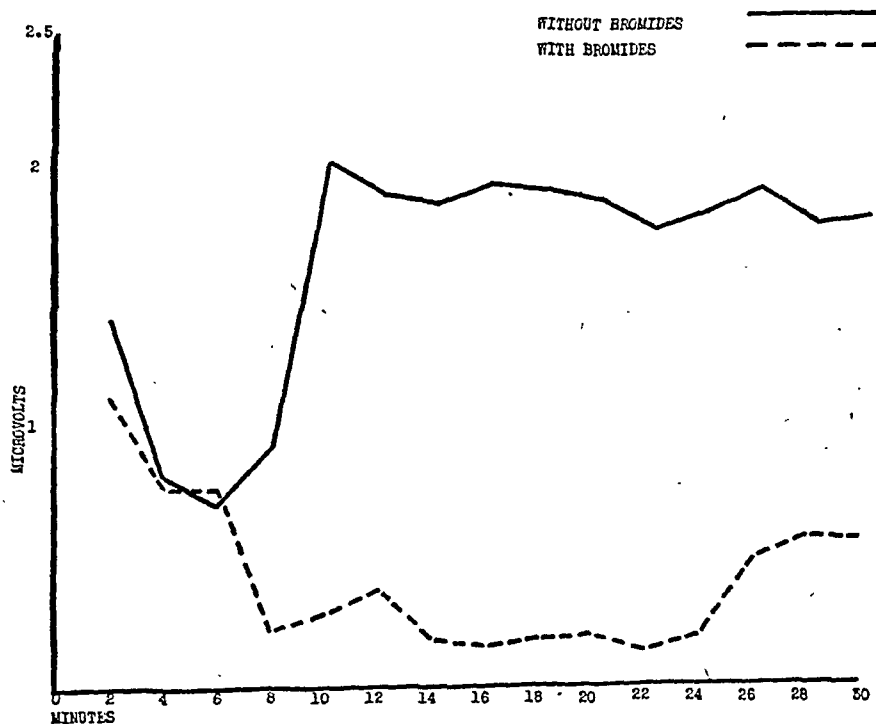


FIG. 1. After the administration of 90 grains of triple bromides by mouth, the curve for subject 14 shows a measured decrease of electrical activity (broken line), as compared with similar tests without medication (unbroken line).

In this and in figures 2, 3, 6 and 7, each curve represents a composite of three 30 minute tests made on different days. In all figures each point is plotted to indicate the micro-voltage averaged for the preceding two minutes.

ably prove sufficiently long for present purposes. No attempt was made to determine the minimum effective dosage, but it was desired if possible to employ with all subjects a uniform dose which might have an observable result in most if not in all instances. Therefore, in a trial experiment with one subject, 30 grains were given by mouth (twice the dose of triple bromides standardized in the National Formulary) but (contrary to the custom in

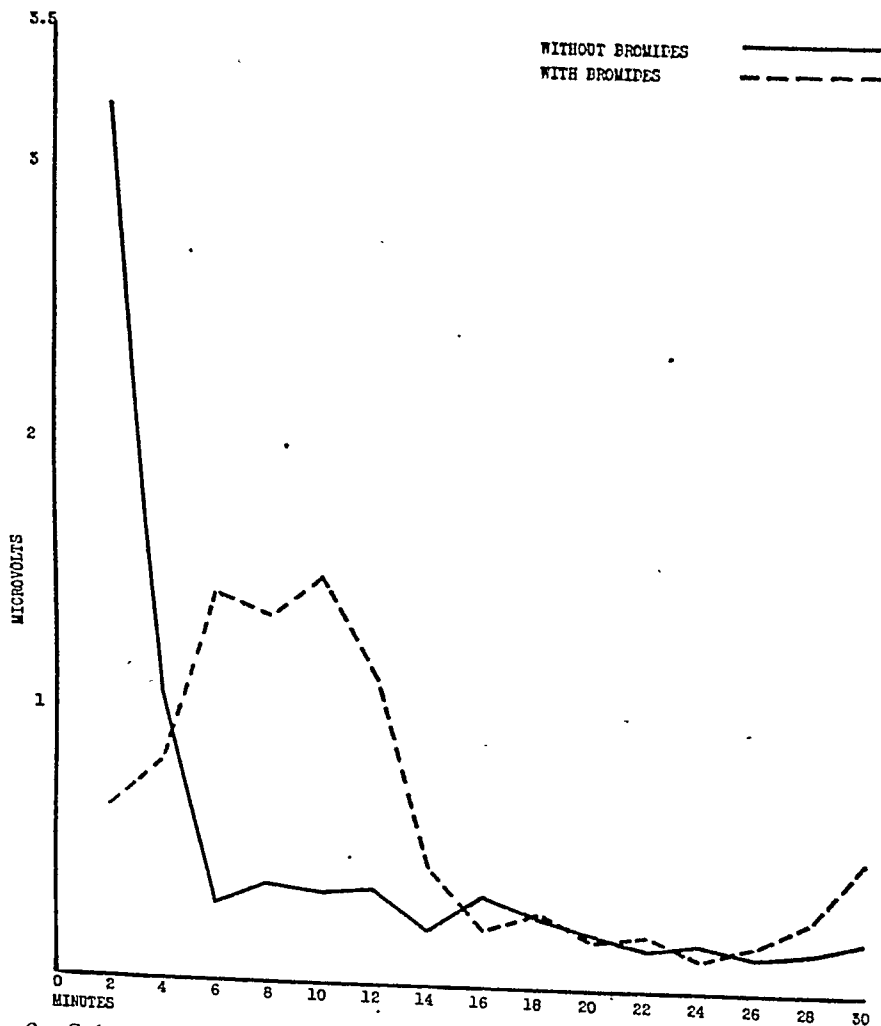


FIG. 2. Subsequent to the administration of 90 grains of triple bromides by mouth, the curve for subject 13 shows measured increase of electrical activity (broken line) after the first four minutes, as compared with similar tests without medication (unbroken line). This increase persists for about 10 minutes, after which the curves show little difference. In this test, no indication of sedation is manifested.

clinical practice) the subject was kept in ignorance as to the nature of the medication. Upon inquiry, he stated that he failed to notice any difference in sensations or in any other respect as compared with times when he had taken no medicine. Accordingly, it was decided to administer six times the standard clinical dosage by mouth, namely 90 grains, half two hours before the test and half one hour before the test.



When this was done contraction-potentials were lowered moderately in most instances as compared with control tests made on different days, in which no medication at all was given, but in which every other procedure and condition present on test days was duplicated as far as possible. Subjective effects were less marked than would generally be anticipated; two subjects complained of a little dizziness; several stated that, judging by their feelings, they would not have known that they had taken any medicine at all.

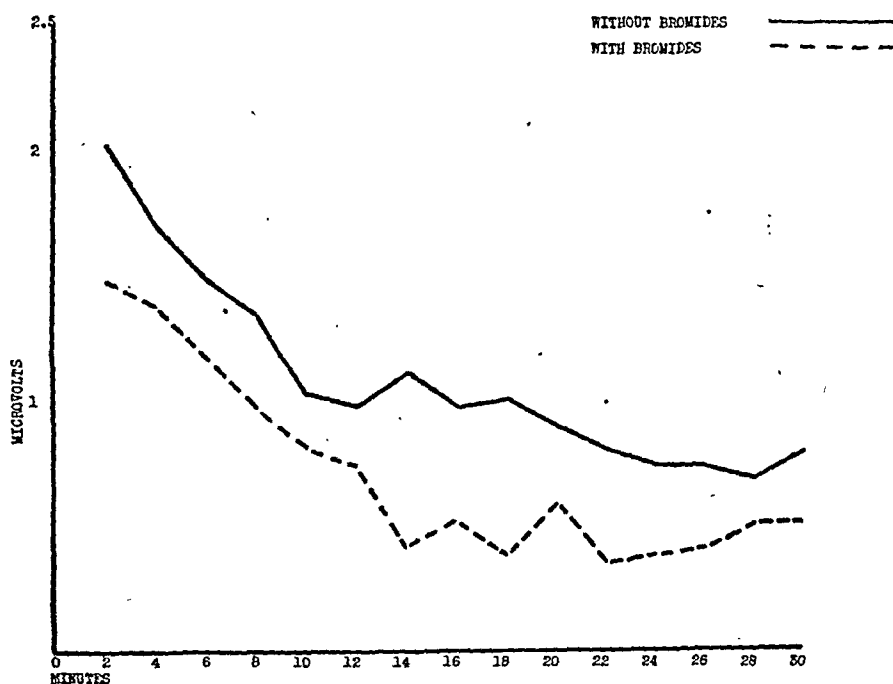


FIG. 3. Following the administration of 90 grains of triple bromides by mouth, the composite graph for 15 subjects shows a measured decrease of electrical activity (broken line), as compared with similar tests without medication (unbroken line).

A half-hour recording was made on each subject on three different days following the administration of bromides, and a control test under similar conditions but without medication was made on each of the three intervening days. For each half-hour of test, the average integrated action-potential value is found for each two-minute period and the average of these averages is then calculated for the three tests, both with and without bromides (table 1, columns 4 and 5). Comparing these values, a decline followed the administration of bromides in 11 of the 15 instances, but an increase in the four others. (In two of the instances of decline as well as in two of the instances of increase, the change was less than 10 per cent.)

The curve for the most marked instance of decline for any subject is shown in figure 1,\* and one showing an increase for about one-third of the

\* Subjects requested to sit quietly for a prolonged period often exhibit a rise of integrated action-potentials after the lapse of a variable interval. They report that they become impatient and desire to move about. This might explain the rise of the unbroken line

period and an approximate equality for most of the remainder appears in figure 2. Evidently even following six times the standard dosage of bromides, the effect can be manifestly negative in exceptional instances under the conditions studied.

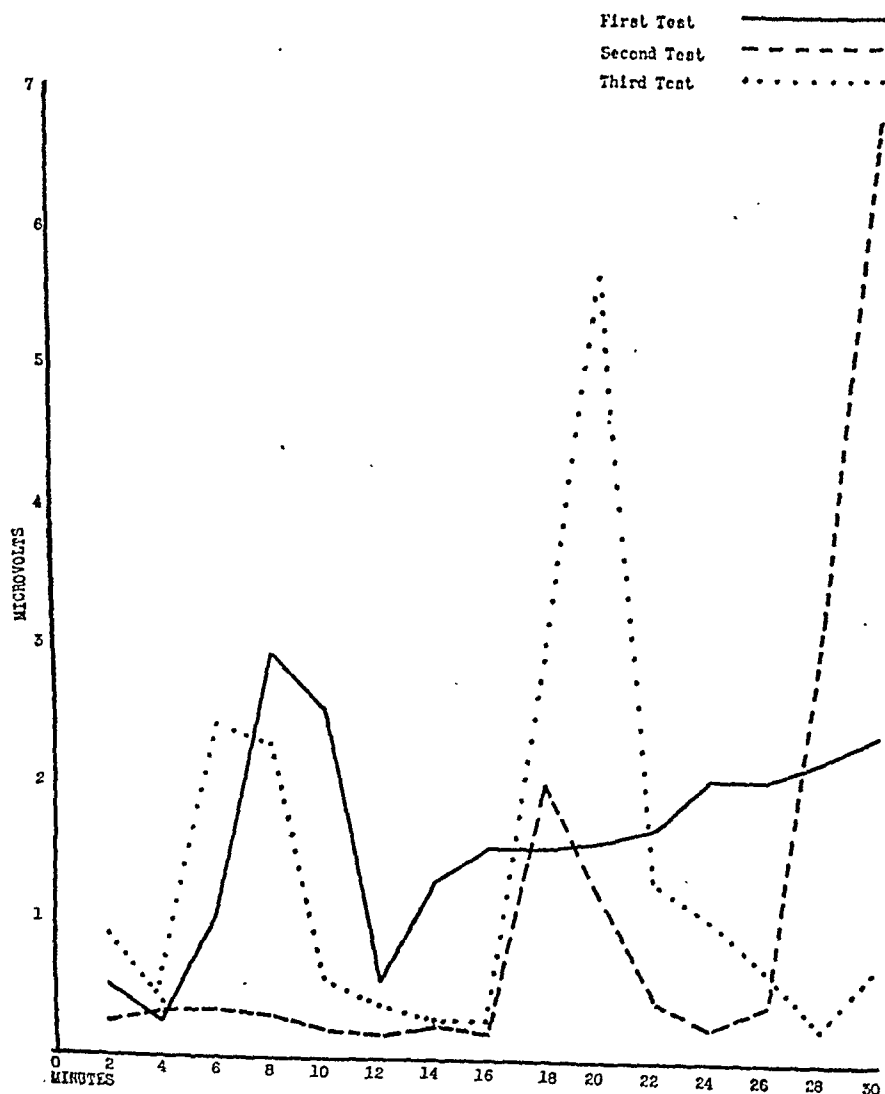


FIG. 4. These curves for subject 15 (plumber) illustrate the character and magnitude of daily variations in control tests (when no medicine was administered).

However, if the results for all subjects are included in a composite graph, a distinct if moderate effect of the bromides is indicated (figure 3). Integrated potentials in the muscles tested are (on the whole) lowered during the period investigated.

The subjects show considerable daily variation in the unmedicated control at 10 minutes and thereafter seen in figure 1. The effect of the sedative might be to nullify this tendency toward increased tension, indicated by increased action-potentials, so that it fails to appear in the curve following medication.

dition, but when the results are positive the tendency of the sedative seems to smooth out the curve somewhat. This is illustrated in one subject by the individual curves for three different days without bromides shown in figure 4, in comparison with those for three intervening days on which bromides were given shown in figure 5. The integrated action-potential is diminished in its average value as well as in its degree of variation following ingestion of the bromides in the dosage stated.

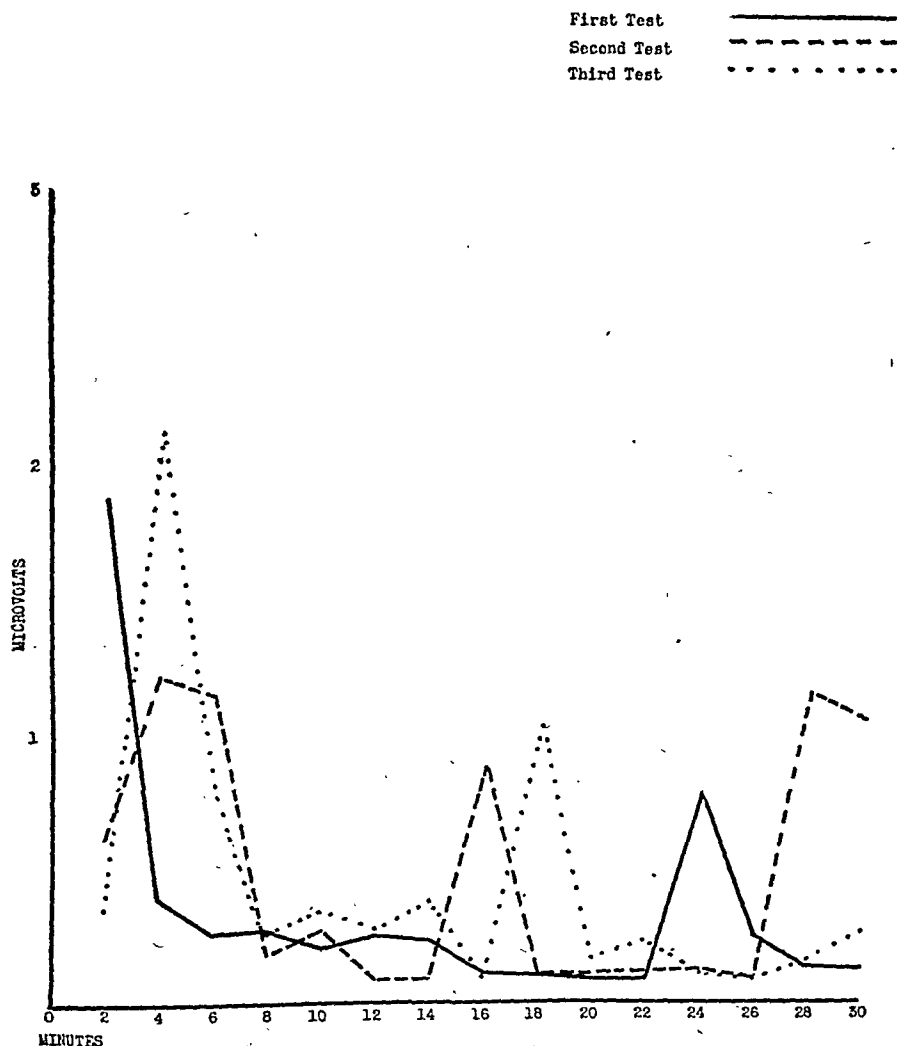


FIG. 5. In these curves for the same subject as in figure 4 but on intervening days, following the ingestion of bromides, the integrated action-potential averages less and the daily variation is diminished.

At the beginning of many of the observation periods, a relatively large drop in integrated potential occurs. This presumably marks the individual's becoming more relaxed as he adapts himself to the conditions of test, as discussed previously. In some instances (as in the control test in figure 1), the adaptation proves shortlasting.

TABLE II

Results in subject 15. Figures in the first two rows indicate the range of microvoltage variation in each test. Those in the third row show the mean values of the determinations for tests indicated by the headings of the columns. Variance and probable errors appear in the fourth and fifth rows.

		Without Bromide				With Bromide				Sterile Water			
		Test No. 1	Test No. 2	Test No. 3	Total	Test No. 1	Test No. 2	Test No. 3	Total	Test No. 1	Test No. 2	Test No. 3	Total
Range	{ High Low	2.92	6.77	5.66		1.88	1.24	2.12		4.32	.49	4.10	
Mean		.24	.16	.24		.09	.09	.10		.11	.09	.13	
P.E.		1.59	1.08	1.32	1.33	.34	.48	.45	.42	.97	.16	1.36	.83
		.77	1.76	1.57	.91	.46	.47	.54	.32	1.33	.11	1.33	.68
		.134	.306	.173	.158	.080	.082	.094	.056	.231	.019	.231	.118
		Caffeine				Sodium Amytal							
		Test No. 1	Test No. 2	Test No. 3	Total	Test No. 1	Test No. 2	Test No. 3	Total				
Range	{ High Low	3.47	6.92	5.00		1.86	.81	1.73					
Mean		.27	.30	.45		0	.03	.11					
P.E.		1.36	2.23	1.89	1.83	.22	.24	.47	.31				
		1.006	1.84	1.64	1.29	.46	.17	.47	.29				
		.175	.320	.285	.224	.080	.030	.082	.050				

The range of daily variation is illustrated also by the data secured for one subject (No. 15) as shown in table 2 (rows 1 and 2). In the third row appear the mean values, while the variance and probable error of the mean appear in the remaining rows. These values are calculated according to standard formulae, namely,

$$\sigma X = \frac{\Sigma(X - \bar{X})}{N - 1} \quad \text{and} \quad \text{P.E. of } \bar{X} = \frac{.6745X}{\sqrt{N}}$$

For this subject the total value with bromide (.42) is much less than the corresponding value without bromide (1.33). The reduction is more than five times the probable error of the mean, a result which is clearly significant.

Another set of tests was conducted similarly, except that sodium amytal was administered intramuscularly and the effect measured beginning one-half hour later. The dosage, grains  $1\frac{7}{8}$  was selected as unlikely to interfere with the subjects in their daily work. However, subjective effects such as sleepiness seemed considerably greater than those following the bromides. We can compare the averaged values for the barbiturate (determined as stated above) with those determined on intervening days, when sterile water was injected, assuming that our control conditions should as far as possible duplicate the tested conditions. To this end the tests following bromides administered by mouth were generally alternated on successive days with tests without medication, and the tests following injections were also grouped together in point of time as far as possible. It is possible that the injection of a solution has psychological effects which should be considered. There-

fore, we assume that the results following the injection of barbiturate and of caffeine are comparable with the injection of sterile water, rather than with those labeled "Without Bromides." Otherwise, admittedly, if the sterile water figures are taken as a control, the effect of the bromide appears not to be significant.

Comparing the results for the 15 subjects following the administration of sodium amytal as stated above, 13 showed declines, but four of the latter

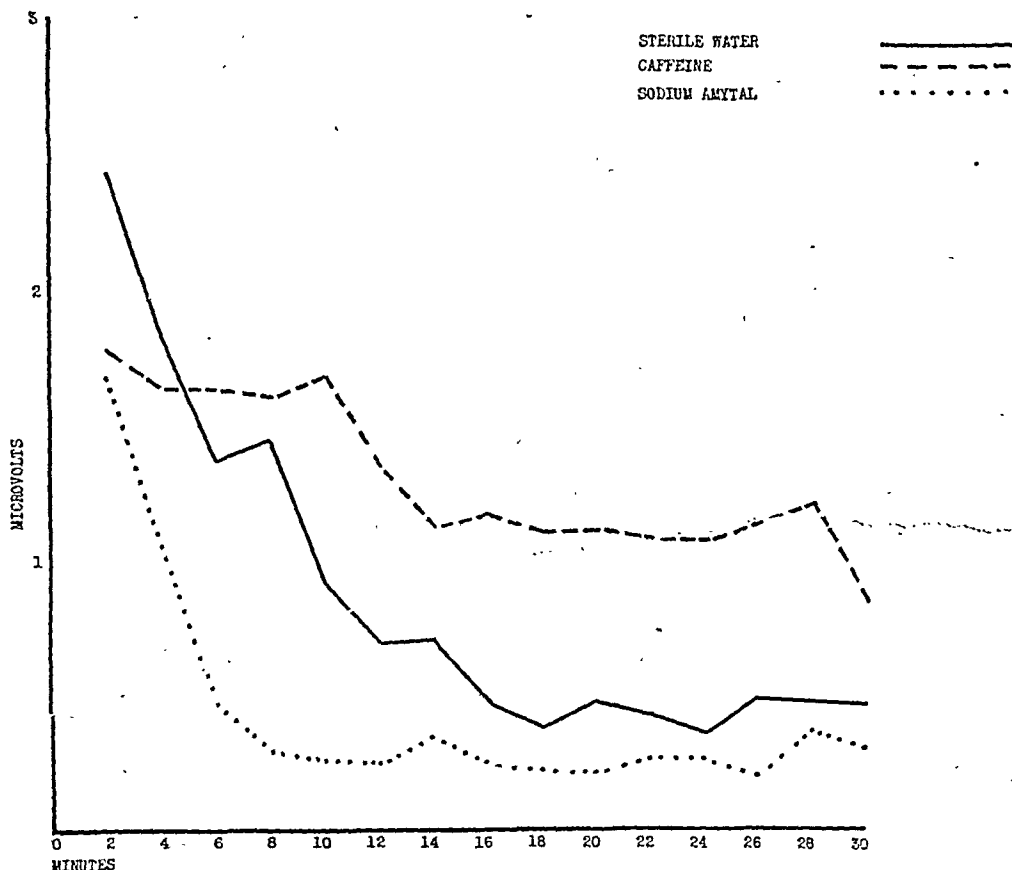


FIG. 6. Following the intramuscular injection of  $1\frac{7}{8}$  grains sodium amytal, the composite graph for 15 subjects shows a measured decrease of electrical activity (dotted line) as compared with the results following a similar injection of sterile water (unbroken line). Following the intramuscular injection of  $7\frac{1}{2}$  grains caffeine sodium benzoate, the graph (broken line) shows a measured increase of electrical activity, as compared with the control (unbroken line).

were below 10 per cent. The other two subjects showed increases exceeding 10 per cent. These results are revealed in the averages shown in table 1, column 6, which can be compared with the averages for the controls (sterile water) shown in column 7.

If the results for all the subjects are included in a composite graph, a distinct decline in contraction-potentials is obvious, as compared with the graph for the control tests following injections of sterile water (figure 6).

The composite graph following the intramuscular administration of sodium amytal (gr.  $1\frac{7}{8}$ ) indicates distinctly lower contraction-potentials than that following the oral administration of the bromides (gr. 90).

In subjects whose control tests show little tonicity, the reduction effected by the barbiturate may reduce the contraction practically to zero level. This is illustrated in figure 7, where the composite values for subject 5 are shown, following the injection of sodium amytal as well as of sterile water. We

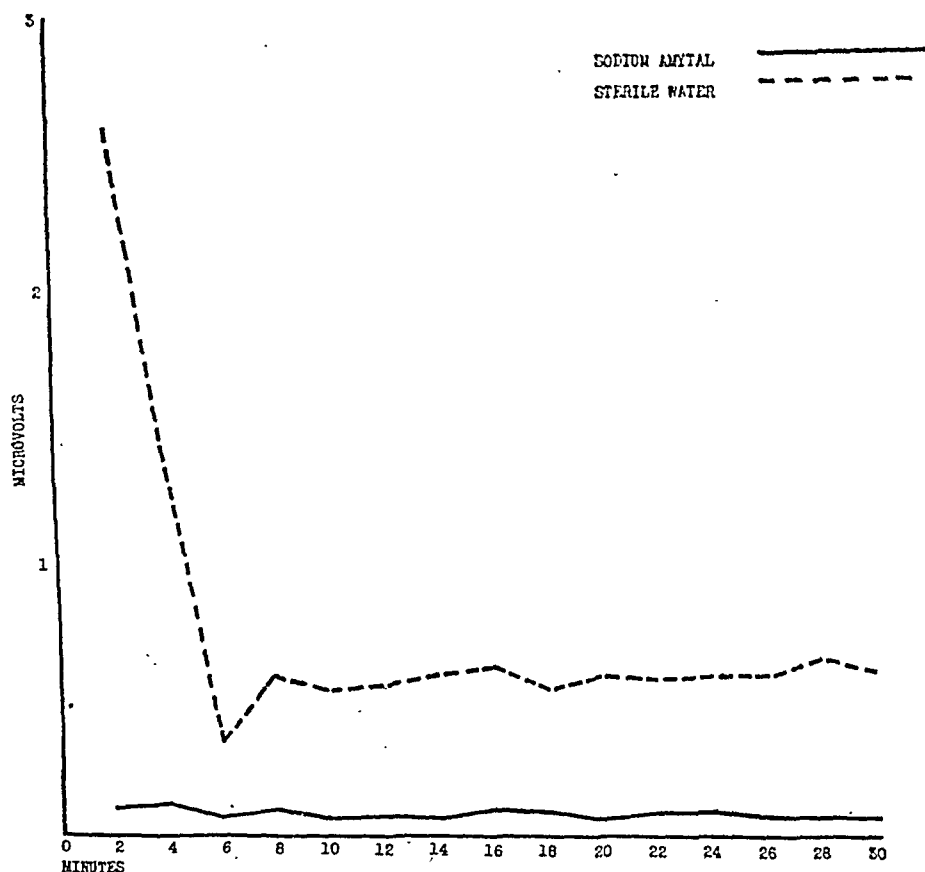


FIG. 7. Following the intramuscular injection of  $1\frac{7}{8}$  grains sodium amytal, the composite graph for three tests for subject 5 shows a measured decrease of electrical activity approximately to the zero level (unbroken line), as compared with the results following the injection of sterile water (broken line). Conditions as in figure 1.

can assume that probable errors of measurement due to the instrument itself amount to 0.01 microvolt. Accordingly, the tonus level for this subject following the administration of the barbiturate, appears to be approximately but not quite at zero.\*

Caffeine sodium benzoate (gr.  $7\frac{1}{2}$ ) was injected intramuscularly one-half hour before the tests. Few subjective effects were noted. The subjects

\* When the mean of 10 readings, for example, was 17.3 scale divisions per microvolt a.c. impressed upon the amplifier, the probable error of the mean was .15, which is less than 1 per cent.

did not fall asleep as often following the administration of this stimulant as they did following that of the bromides and particularly that of the barbiturate. At least one, however, fell asleep during the test (subject 12 in table 1).

A marked increase of contraction-potentials following the administration of caffeine (as compared with that of sterile water) is noted for most subjects. Of the 15 subjects, 14 show an increase and for all but one the increase exceeds 10 per cent. One shows greater relaxation following the caffeine than following the sterile water injection. All subjects were mostly habitual coffee drinkers.

The composite graph for the results following the administration of caffeine appears in figure 6. The stimulating action is evidently measurable by the present method.

The range of daily variation following the administration of caffeine and sodium amytal as compared with sterile water can be illustrated once more with one subject (No. 15), as shown in rows 1 and 2 of table 2. Under the corresponding headings in the third row appear the mean values; the variance and the probable error of the mean appear in the remaining rows. For this subject the total mean value following the injection of sterile water is .83, and that following the injection of caffeine is 1.83. The increase is more than four times the probable error. Following the injection of sodium amytal the total mean value is reduced to .31, a reduction which is more than four times the probable error. The figures can be interpreted as indicating a significant increase in the contraction-potentials following caffeine and a decrease following sodium amytal, in both instances compared with the control following the injection of sterile water.

Subjective complaints were most frequent concerning the effects of the sterile water. One individual (subject 7, table 1) stated that the injection led to fainting spells such as he had not experienced since boyhood. Apparently in all subjects there was a tendency for "burning" sensations to develop at the site of injection of the water. Perhaps this might have been averted if physiological saline solution had been employed instead.

#### DISCUSSION

Quantitative measurements can be applied to the nervous system directly. For this purpose, an electrode is inserted into any nerve at some locality near the surface, for example the ulnar nerve in the fossa adjacent to the olecranon process. This procedure has been outlined previously.<sup>6</sup> Following my experience with these methods, there is no reason to assume that results so secured would differ in the gross from those presented herein, but extension of the investigation in this direction is indicated.

It seems irrelevant to review here countless previous investigations on the effects of stimulants and sedatives, whatever their importance, inasmuch as the results have been chiefly in terms of reactions of the organism or of

changed bodily chemistry. Changes in the electroencephalogram following the administration of drugs have engaged the attention of various investigators since the time of Berger.<sup>7</sup> Stimulants such as caffeine may or may not produce a direct, registrable effect on brain waves, but sedatives will do so, provided they induce a somnolent state (Berger). "Sedatives cause changes similar to those observed in normal sleep" (Gibbs et al.). However, the qualitative variations between individuals are considerable,<sup>8</sup> the source of the waves not yet certain,<sup>9</sup> and the effects of drugs provide additional variations affording little hope of securing data of quantitative significance. No one up to date has suggested that brain wave recordings yield data suitable for the quantitative registration of the influence of stimulants or sedatives on the nervous system.

### SUMMARY AND CONCLUSIONS

1. Direct measurements can be obtained of the effects of stimulants and sedatives (and other types of medication) on the muscular and nervous systems in terms of action-potentials, if suitable electrodes are placed in neuromuscular regions.

2. Measurements should be accurate to a very small percentage of a microvolt d.c. within a selected frequency range. For quantitative purposes, the Integrating Neurovoltmeter (or Myovoltmeter) is most convenient. Potentials in muscle during a period of test can be averaged for unit periods and plotted in microvolts d.c. against time. In the present investigation this was done for the flexor muscles of one arm in 15 subjects in a fair state of health. The data apparently can afford some index of the influence of stimulants and sedatives on the effector portion of the nervous system.

3. Bromides by mouth in customary dosage (15 grains) would appear to have little if any measurable effect on some normal individuals according to the present test. This suggests that therapeutic results from such small doses probably often depend upon the knowledge of the patient that he has taken a sedative.

4. Bromides in large dosage (90 grains within two hours) affected some of the individuals tested but little, if at all. However, according to the subjective reports as well as the objective findings, the composite graph for the 15 subjects shows diminished potentials as compared with controls when no medication was given.

5. A greater quieting effect on the neuromuscular system was notable in the composite results following the intramuscular administration of sodium amytal (grains  $1\frac{7}{8}$ ).

6. Caffeine sodium benzoate (grains  $7\frac{1}{2}$  intramuscularly) produced little effect in some instances, but a definitely stimulating effect was noted in the composite graph, as compared with the results following the injection of sterile water.



## BIBLIOGRAPHY

1. JACOBSON, E.: (a) The direct measurement of nervous and muscular states with the integrating neurovoltmeter (action-potential integrator), *Am. Jr. Psychiat.*, 1940, xcvi, 513; (b) An integrating voltmeter for the study of nerve and muscle potentials, *Rev. Sci. Instr.*, 1940, xi, 415; (c) Recording action-potentials without photography, *Am. Jr. Psychol.*, 1941, liv, 266.
2. WESTPHAL, C.: Ueber einige Bewegungs-Erscheinungen an gelähmten Gliedern, *Arch. f. Psychiat.*, 1875, v, 803; ERB, W.: Ueber Sehnenreflexe bei Gesunden und bei Rückenmarkskranken, *Arch. f. Psychiat.*, 1875, v, 792; MITCHELL, S. W., and LEWIS, M. J.: The tendon-jerk and muscle-jerk in disease and especially in posterior sclerosis, *Trans. Assoc. Am. Phys.*, 1886, i, 11; JACOBSON, E., and CARLSON, A. J.: The influence of relaxation upon the knee-jerk, *Am. Jr. Physiol.*, 1925, lxxiii, 324.
3. JACOBSON, E., and KRAFT, F. L.: Contraction potentials (right quadriceps femoris) in man during reading, *Am. Jr. Physiol.*, 1942, cxxxvii, 1.
4. JACOBSON, E.: Electrical measurements concerning muscular contraction (tonus) and the cultivation of relaxation in man. Studies on arm flexors, *Am. Jr. Physiol.*, 1934, cvii, 230; Electrical measurements concerning muscular contraction (tonus) and the cultivation of relaxation in man. Relaxation-times of individuals, *Am. Jr. Physiol.*, 1934, cviii, 573; The course of relaxation in muscles of athletes, *Am. Jr. Psychol.*, 1936, xlviii, 98; The effect of daily rests without training to relax on muscular tonus, *Am. Jr. Psychol.*, 1942, lv, 248; "Tonus" in striated muscle, *Am. Jr. Psychol.*, 1943, lvi, 433.
5. ADRIAN, E. D., and BRONK, D. W.: Discharge of impulses in motor nerve fibers; frequency of discharge in reflex and voluntary contractions, *Jr. Physiol.*, 1929, lxxvii, 119.
6. JACOBSON, E.: Measurement of the action-potentials in the peripheral nerves of man without anesthetic, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 713.
7. BERGER, H.: Über das Elektrenkephalogramm des Menschen, *Arch. f. Psychiat.*, 1934, cii, 538; GIBBS, F. A., GIBBS, E. L., and LENNOX, W. G.: Effect on the electro-encephalogram of certain drugs which influence nervous activity, *Arch. Int. Med.*, 1937, lx, 154; BERGER, H.: Über das Elektrenkephalogramm des Menschen, *Arch. f. Psychiat.*, 1935, ciii, 452; ANDREWS, H. L.: Brain potentials and morphine addiction, *Psychosom. Med.*, 1941, iii, 399; FOWLER, O. D.: Neurophysiological and psychological changes induced by certain drugs; electrocortical changes, *Jr. Exper. Psychol.*, 1941, xxviii, 37; LENNOX, W. G., GIBBS, F. A., and GIBBS, E. L.: Effect on electro-encephalogram of drugs and conditions which influence seizures, *Arch. Neurol. and Psychiat.*, 1936, xxxvi, 1236.
8. DAVIS, H., and DAVIS, P. A.: Action-potentials of brain in normal persons and in normal states of cerebral activity, *Arch. Neurol. and Psychiat.*, 1936, xxxvi, 1214; ANDREWS, H. L., and JASPER, H. H.: Human brain rhythms. I. Recording techniques and preliminary results, *Jr. Gen. Psychol.*, 1936, xiv, 98.
9. ADRIAN, E. D., and YAMAGIWA, K.: The origin of the Berger rhythm, *Brain*, 1935, lviii, 323; HOAGLAND, H.: Pacemakers of human brain waves in normals and in general paretics, *Am. Jr. Physiol.*, 1936, cxvi, 604; HADIDIAN, Z., and HOAGLAND, H.: Chemical pacemakers for alpha brain wave frequencies in general paresis, *Am. Jr. Physiol.*, 1939, cxxvi, 517; BISHOP, G. H.: Abstract of Discussion, *Arch. Neurol. and Psychiat.*, 1936, xxxvi, 1246; SPEIGEL, E. A.: Abstract of Discussion, *Arch. Neurol. and Psychiat.*, 1936, xxxvi, 1248.

# SOME CLINICAL CHARACTERISTICS OF MUMPS, AND THE EFFECT OF BELLADONNA IN TREATMENT; A STUDY MADE AT THE STATION HOSPITAL, FORT GEORGE G. MEADE, MARYLAND\*

By HAROLD W. POTTER, F.A.C.P., LT. COL., MEDICAL CORPS, ORC, and  
LEWIS H. BRONSTEIN, CAPT., MEDICAL CORPS, A. U. S.

IN civilian practice mumps is considered a disease of children and, therefore, is not considered much of a problem from the standpoint of disturbing the life of a community. The adults who contract the disease are usually the butt of jokes of their friends and are infrequent enough to cause comment only from that standpoint.

In military life, however, mumps may become much more of a problem, not from a disabling standpoint, but from the fact that it might fill hospital beds which are needed for other types of sick patients. The length of time the soldier has to stay in the hospital also causes interference with the training program that his organization is undertaking.

The study of the following consecutive 124 cases was originally undertaken in an attempt to ascertain the value of treating such patients with belladonna. The use of this drug had been suggested to shorten the course of the disease and to decrease the incidence of complications. The study of these cases revealed some facts at variance with previous recorded material in the literature, as well as confirmation of other statements. Future studies of more cases may either confirm or discount these observations. However, it is hoped that this will give impetus to more observation in a disease which has been accepted in most quarters as "just one of those things."

Excellent reviews of this disease<sup>1, 2</sup> are present in recent literature. It is deemed unnecessary, therefore, to discuss all the aspects of the condition.

All of these cases were not suitable for every type of analysis. In some instances, for example, the exact date of determination of the swelling could not be determined from the clinical record. In determining the incidence of orchitis, the members of the W.A.A.C. who had mumps were excluded because none of them had oöphoritis and because oöphoritis is a rarer complication than orchitis.

*Effect of Belladonna.* Forty-two consecutive cases of mumps were treated with belladonna and were compared with the previous 82 cases which were not so treated. The untreated cases were seen from October 1942 through March 1943 and the treated ones from March 1943 through May 1943.

\* Received for publication August 16, 1943.

A preliminary analysis of the 82 untreated cases showed no significant difference, as far as duration of disease was concerned, in those patients who entered with a unilateral lesion which did not spread, with a unilateral lesion which became bilateral, or with a bilateral lesion. The comparison was, therefore, made only in regard to the day of the disease on which the soldier entered the hospital. There were too few cases in the belladonna series who entered on the third day or subsequent day for adequate comparison of duration of illness. Accordingly, only the series for the first and second day were compared.

The medication was administered as follows: On admission, the soldier was given gr. 1/100 of atropine sulfate and then 1 c.c. of the tincture of belladonna by mouth every two hours, until atropinization, as evidenced by dilatation of the pupil and/or dryness of the throat, was produced. Subsequent medication was given in doses to keep these changes constant, either until the patient was cured or until gastrointestinal discomfort made it necessary to discontinue the drug. The 1 c.c. was measured out by hypodermic syringe in order to have as accurate a dose as possible.

The patients who received belladonna had as much discomfort from their parotitis as did those who did not receive the drug. In addition, some had abdominal distress from the high dosage of drug that had to be given.

TABLE I  
Duration of Illness—Treated with Belladonna and Untreated

	No. of Cases	Mean No. of Days	Standard Deviation	Probable Error
A. Admitted to hospital on first day of illness				
Untreated.....	24	11.71	3.3	0.46
Treated.....	11	11.00	3.69	0.62
B. Admitted to hospital on second day				
Untreated.....	33	13.3	4.18	0.491
Treated.....	16	12.8	2.76	0.165

A study of table 1 will show that there is no statistical significance to the difference between the durations of the disease in these groups.

In each series of cases there was one case of meningo-encephalitis. Table 2 A shows the incidence of orchitis in the two series. In this grouping, the females were excluded as were those patients who entered the hospital with orchitis. A comparison of the percentages by means of either the standard or probable error method shows that no statistical significance can be attached to the difference between them.

Table 2 B shows the average duration of the orchitis if we again include those patients who entered with this complaint. Again no significance can be attached to this difference.

TABLE II

	Total No. of Cases	No. of Cases Developing Orchitis	Percentage Incidence
A. Development of Orchitis			
Untreated.....	77	7	9
Treated.....	35	6	17.1
B. Duration of Orchitis*			
	No. of Cases	Mean Duration	
Untreated.....	11	8.7	
Treated.....	8	7.0	

\* In one case who entered with orchitis and parotitis, the day of termination of illness could not be determined.

It is thus apparent that belladonna given as indicated above had had no effect in cases of mumps on the following events in the course of the disease: (1) duration of illness; (2) incidence of complications; (3) duration of orchitis; (4) comfort and well being of the patient.

*Origin and Race of the Soldier.* The largest series of cases to be published from studies in young adults was from World War I.<sup>3</sup> The statement was made that most of the soldiers came from rural communities. This statement has been repeated time and time again and has been quoted as late as 1940.<sup>1, 2</sup> We, therefore, reviewed our cases from that standpoint.

It is rather difficult to decide where to place the boundary between rural and urban communities. We used the home address of the soldier as well as his civilian occupation in an attempt to decide in which category he should be placed. It was decided that a town's population of 10,000 would be a dividing line. It is realized that this probably helps throw the weight of the figures to the rural group. In addition, many soldiers who had migrated to a city to work have no permanent address there and are more likely to give their parents' address which might be in a small community. It is with this knowledge that the results are more unusual in that 50 soldiers came from urban areas and 72 came from rural areas. One soldier gave his address as no home and information was lacking in another.

The cases were broken down to determine the race of the soldier and his origin. Table 2 shows that there were twice as many white as colored soldiers admitted with mumps. However, the population of the camp had a much greater proportion of white to colored soldiers during this time so that there is a greater incidence among the colored soldiers, as has been noted previously. From the same table, it can also be seen that the colored soldiers had a preponderance of rural origin as compared to the white soldiers. The greatest majority of these men came from the Southern states.

These figures indicate that in our series there was not the great difference noted previously between rural and urban groups. This difference is gradually being destroyed with our changes in civilization, such as improved methods of transportation, consolidated school systems in rural areas, etc., which make for greater contact among people. The group which is still isolated to the greater degree from the standpoint mentioned above are the negroes of the South. The figures show that some distinction between rural and urban populations holds. However, it is not as marked as previously recorded. Should analysis of a larger series of cases bear out this finding, a change in our concept should be recorded in textbooks and literature.

*Duration of Service.* With an ever-expanding Army, there is a continuous influx of new recruits into the service so that communicable disease should always find a fertile field in which to spread. Wheelis,<sup>4</sup> in considering this factor for communicable disease generally, found that the highest rates occurred during the first two months of military service. However, he advises study for individual disease. Ravdin,<sup>3</sup> in discussing the mumps cases at Camp Wheeler during World War I, states that the length of service in 95 per cent of the cases was two months. Our cases were, therefore, considered from this standpoint.

In analyzing the figures it became apparent that there were two ways of viewing them. It was possible merely to take the length of the soldier's service in the Army at the time he developed his mumps. Table 3 shows

TABLE III\*  
Color and Origin

Total No. of Whites	Rural	Urban
80	42	37
43	30	13
Colored		
43	30	13

\* One case record not complete. One white patient had no address.

this in column 1 in relation to intervals of two months' service. However, such a table would not take into account those soldiers who entered during the summer when mumps was not prevalent. Our cases ran from October through May. There were only two cases during the last week of October. The cases really began to come in in November. That month was, therefore, chosen as the first month of the mumps season and the duration of service was related to November 1942. Thus, a soldier who came down with mumps in January 1943 and had six months' service was credited as having only three months' service. Obviously, those soldiers who had one or more years' service were credited with their full time. This correction is seen in column 3. The appropriate percentages can be found in columns 2 and 4.

These figures show that our series of cases do not follow the expected relationship as recorded in the literature. The uncorrected series shows that 26.66 per cent of the cases had only four months' service and 39.46 per cent one half year's service. The largest groups were those with eight and 10 months' service. The corrected series shows that 41.66 per cent of the cases had four months' service and 58.32 per cent had up to six months' service. In both groups, approximately 85 per cent had their mumps within the first year.

It would seem that the time limit for developing mumps in susceptibles should be extended from two months to one year in order to include all of them. This longer exposure may be due to a slightly acquired resistance with greater urbanization in the years following World War I. This would fit in with the previous facts that urban or rural distribution has changed. However, more cases are necessary to verify this.

*Duration of Disease.* It was thought that the day of hospitalization and therefore beginning of treatment would have some effect on the duration of the disease. Our treatment, including those who were tested with belladonna, consisted of regular diet, mouth wash where indicated, and absolute bed rest, which was not always observed by the soldier.

TABLE IV\*  
Relation between Onset of Mumps and Duration of Service \*

	I Uncorrected	II Percentage	III Corrected to November 1942	IV Percentage
Up to 0-2 months.....	16	13.33	25	20.83
Up to 4.....	16	13.33	25	20.83
6.....	15	12.50	20	16.66
8.....	26	21.66	13	10.83
10.....	22	18.33	15	12.50
12.....	7	5.83	5	4.16
14.....	2	1.66	2	1.66
16.....				
18.....	1	0.83	1	0.83
20.....	1	0.83	1	0.83
22.....	3	2.50	3	2.50
24.....	5	4.16	5	4.16
26.....				
28.....	3	3.50	3	2.50
1-3 yrs.....	2	1.66	2	1.66
4 yrs.....	1	0.83	1	0.83

\* Four cases omitted—one case, length of service was not recorded. Three cases were admitted to hospital on first day in Army with mumps having been present for four, five, and nine days.

Table 5 was set up with this in mind. It shows that there is no significant difference if the cases that entered the hospital on the first, second, and third days are considered. Those who entered on subsequent days were too few in number to help from a statistical standpoint. The known num-

TABLE V  
Relation of Day of Hospitalization to Duration of Disease

	No. of Cases	Mean	Standard Deviation	Probable Error
1st Day.....	41	11.4	3.57	0.37
2nd Day.....	49	13.1	3.67	0.353
3rd Day.....	12	13.5	2.94	0.6

ber of days is the total number that the soldier had his disease. If only the days of hospitalization are considered, no significance can still be detected.

*Miscellaneous.* The total incidence of orchitis was 11.6 per cent, considering only those who developed this complication after entering the hospital. This is not significantly lower than that reported in the various larger series of cases. However, all our patients who developed orchitis had involvement of both parotid glands before they developed the orchitis. This might mean that they had to have a greater dissemination of virus before that complication developed. However, we only had 13 such cases, too few to make any generalization about this.

All our cases developed temperatures reaching 103° to 104° F. when the orchitis appeared. They appeared quite sick at this time. This is in harmony with other reports.<sup>1, 3</sup>

#### SUMMARY AND CONCLUSIONS

1. One hundred twenty-four cases of mumps occurring in soldiers are reported.

2. Belladonna was used in treating 42 of these cases without any effect on the duration of illness, incidence of complications, duration of orchitis, or comfort of the patient.

3. The distinction between rural and urban origin of the soldier is no longer as definite as it was in previously reported series of cases, probably due to decreased isolation of population groups.

4. Most of the men developed mumps within their first year of service and possible exposure and not in the first two months as reported in the World War I.

5. Early hospitalization does not shorten the duration of the disease.

#### BIBLIOGRAPHY

1. WESSELHOEFT, C.: Mumps: Its glandular and neurologic manifestations. Virus and rickettsial diseases, Harvard School of Public Health Symposium, 1940, 309-342.
2. GORDON, J. E., and HEEREN, R. H.: Epidemiology of mumps, Am. Jr. Med. Sci., 1940, cc, 412-428.
3. RAYDIN, M. J.: The epidemic of mumps at Camp Wheeler, Oct. 1917-March 1918, Arch. Int. Med., 1918, xxii, 354-369.
4. WHEELIS, J. M., JR.: A time study of morbidity and mortality in the United States Navy, Am. Jr. Pub. Health, 1938, xxviii, 1291-1297.

# CASE REPORTS

---

## SARCOIDOSIS WITH UVEOPAROTID FEVER \*

By WILLIAM M. M. KIRBY, M.D., and CHARLES D. ARMSTRONG, M.D.,  
*San Francisco, California*

IN 1889 Besnier<sup>1</sup> described peculiar lesions of the fingers, nose, and ears, a syndrome which he called lupus pernio. The sarcoid of Boeck,<sup>2</sup> described 10 years later, consisted of similar lesions of the skin, mucous membranes, and lymph nodes. In 1914 Schaumann<sup>3</sup> made an important contribution when he recognized that the lesions described by Besnier and by Boeck were actually manifestations of the same disease, which he called lymphogranuloma benignum in distinction to Hodgkin's disease, or lymphogranuloma malignum. During the next few years characteristic alterations of the lungs and of the bones were recognized and described by Kuznitsky and Bittorf,<sup>4</sup> and by Jüngling<sup>5</sup> respectively. The widely disseminated nature of sarcoid has been further emphasized in the extensive literature of the past 20 years; lesions have been described in almost every tissue of the body. It is now also recognized that, although unusual, Besnier-Boeck-Schaumann disease is by no means rare.

It is only in the past few years, however, that another obscure syndrome, the febris uveoparotidea subchronica described by Heerfordt<sup>6</sup> in 1909, has been generally regarded as a form of sarcoid. This entity is characterized by fever, bilateral uveitis and parotitis, and palsy of certain of the cranial nerves, most often the seventh. Bruins Slot<sup>7</sup> first suggested in 1936 that, because of the similar pathological picture and the occasional co-existence of Boeck's and Heerfordt's syndromes, uveoparotid fever is merely another form of sarcoidosis. Others, including Longcope and Pierson in this country,<sup>8</sup> have come to the same conclusion, and a number of cases of sarcoidosis with uveoparotid fever have been reported, chiefly in the ophthalmological literature.<sup>9</sup>

The purpose of this report is to describe a case in which the classical clinical features, both of sarcoidosis and uveoparotid fever, are combined in the same patient. This furnishes additional evidence of the identity of the two syndromes.

### CASE REPORT

Mr. G. H., a 25 year old negro shipyard worker, entered the medical ward of the Stanford University Hospitals on January 12, 1943, with the complaint of poor vision of two weeks' duration. Family and past history was not contributory. He had no dyspnea, fever, cough, fatigue or sputum and had no knowledge of exposure to tuberculosis or venereal disease. Five weeks before entry, while working without suitable welding goggles, he developed a steady, severe ache over both eyes. The company first aid worker said that he had received a flash burn, and gave him some

\* Received for publication March 22, 1943.

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California.



eye drops. Two weeks before entry he again noted pain in the eyes while at work and tried the same treatment. The next morning, however, the pain was unabated, and the patient noticed that the left side of his face was paralyzed so that he could not chew on the left, or close his left eye. Eye drops instilled by a private physician relieved his pain but the facial paralysis persisted, diminishing gradually during the next month. His vision became gradually worse, and he was finally seen in the outpatient eye clinic where he was found to have severe bilateral uveitis with synechiae and vitreous opacities, and admission to the hospital was arranged.

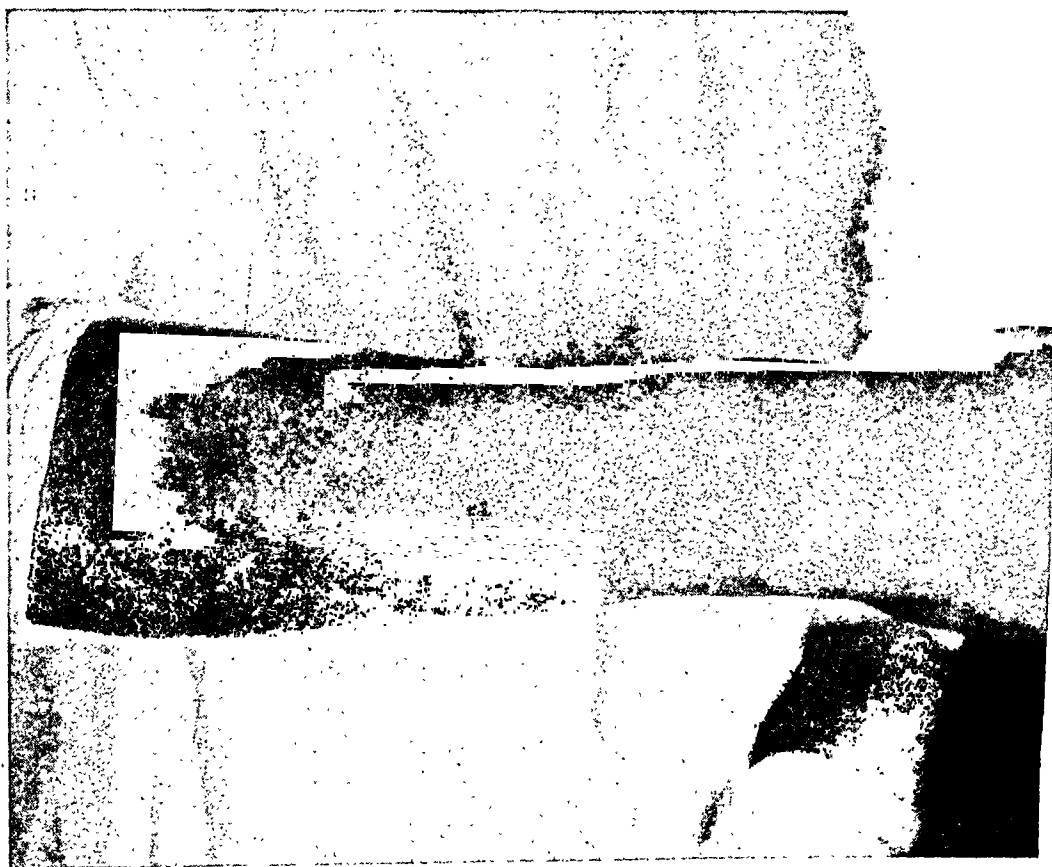


FIG. 1. Sarcoid infiltrations of the skin of the dorsum of the forearm.

*Physical Examination.* On admission the patient's temperature was 38.2° C., pulse 90, respirations 18, and blood pressure 116 mm. Hg systolic and 62 mm. diastolic. The patient was a well developed and nourished young negro who proclaimed himself completely well except for his eyes. The skin in general was moderately ichthyotic, but on the extensor surfaces of both forearms there were numerous 2-3 cm., soft, infiltrated, intracutaneous plaques, none of which had become scarred or depressed (figure 1). There was an infranuclear left facial palsy (figure 2). The pupils were very irregular, fixed to light, and dilated (patient was receiving atropine). Vision was 15/40 in either eye. Heavy, dense posterior corneal opacities could be seen by slit lamp, and there were numerous posterior synechiae. No areas of choroiditis could be seen in the fundus, and there was no increase in intraocular tension.

A firm, non-tender lymph node was palpable in the left pre-auricular region and there were shotty cervical nodes bilaterally; no generalized lymphadenopathy was made out. The breath sounds were somewhat louder over the left chest, but otherwise the heart, lungs, abdomen, and genitalia were not remarkable. The rectum contained no masses or strictures and the extremities and neurological findings were normal except as described.



FIG. 2. Residual left facial palsy, one month after it first appeared. At the time of the photograph he was able to close his eye, but there was still definite weakness of the lower part of the face.

*Laboratory Work.* Blood count on entry showed 4.8 million red blood cells with 80 per cent hemoglobin and 5,600 white blood cells with 70 per cent polymorphonuclears of which 12 per cent were band forms, 20 per cent lymphocytes and 2 per cent monocytes. Total and differential white cell counts were essentially unchanged on three later occasions. Corrected sedimentation rate (Wintrobe) was 20, with a packed cell volume of 40. The urine was normal, and the Hinton and Wassermann reactions were negative.

Tuberculin tests with 0.01 mg. and 0.10 mg. of old tuberculin were negative, but a positive reaction was obtained with 1.0 mg. within 24 hours.

Roentgenogram of the chest (figure 3) showed enlarged hilar and mediastinal nodes with a diffuse granular infiltration of both lungs and these findings were unchanged in a second film taken two weeks later. Roentgenograms of the bones of

the hands, skull, tibiae, and feet showed no abnormalities. Partial gastrointestinal series was normal. Audiograms revealed no hearing defects.

Gastroscopy revealed no mucosal irregularities anywhere which might be interpreted as sarcoid infiltrations. Histological examination of the biopsy of one of the

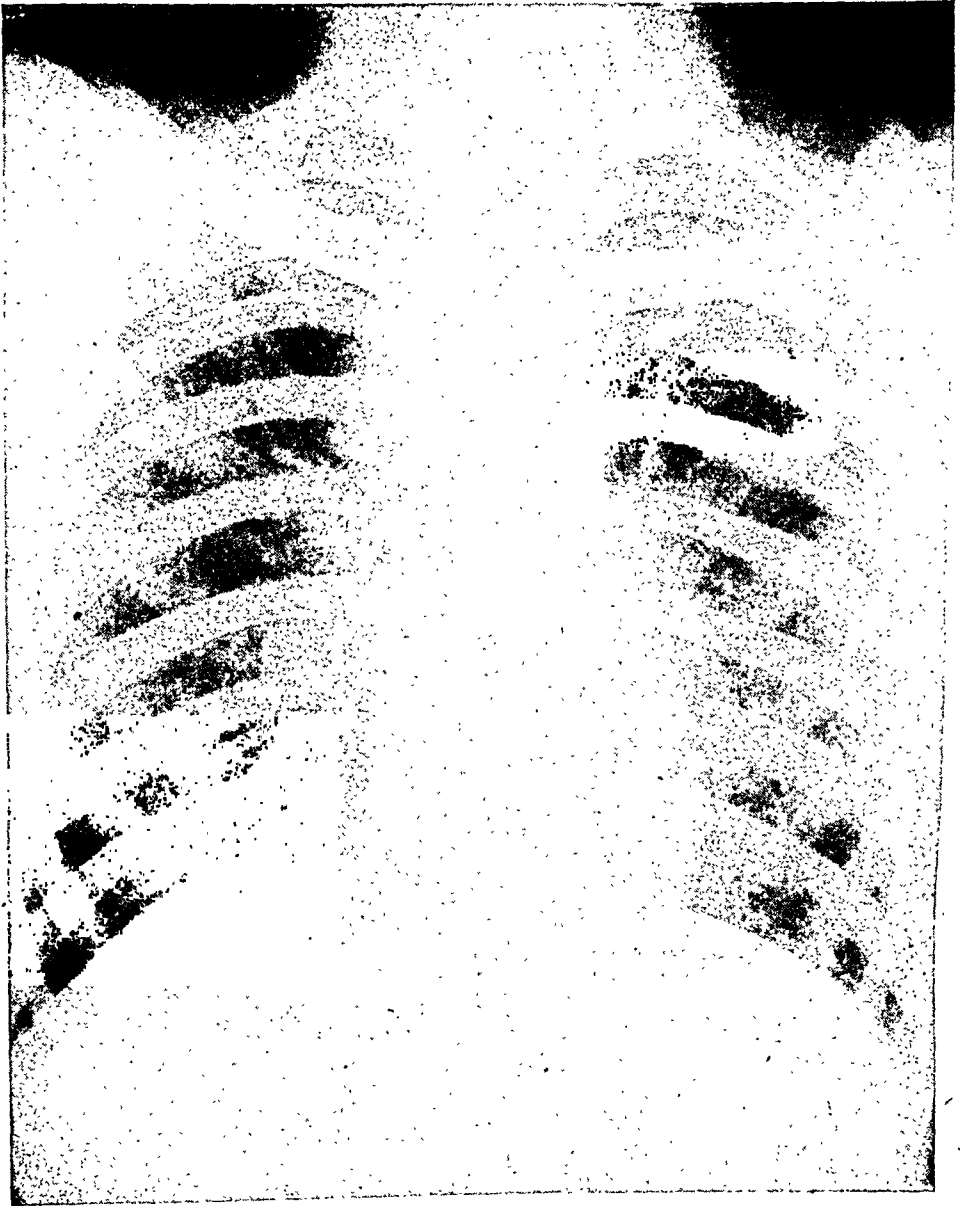


FIG. 3. Chest plate, showing enlargement of the hilar and mediastinal nodes, and granular infiltration of the lung fields.

skin nodules was reported as follows: "The sections of the skin show a stratified squamous epithelium with marked pigment in the basal layer of cells and a few stellate melanoblasts in the superficial corium. There is localized lymphocytic infiltration about the blood vessels and glands of the corium. Deeper in the corium are nodules of epithelioid cells about coiled glands. These can be seen grossly up to 1 mm.

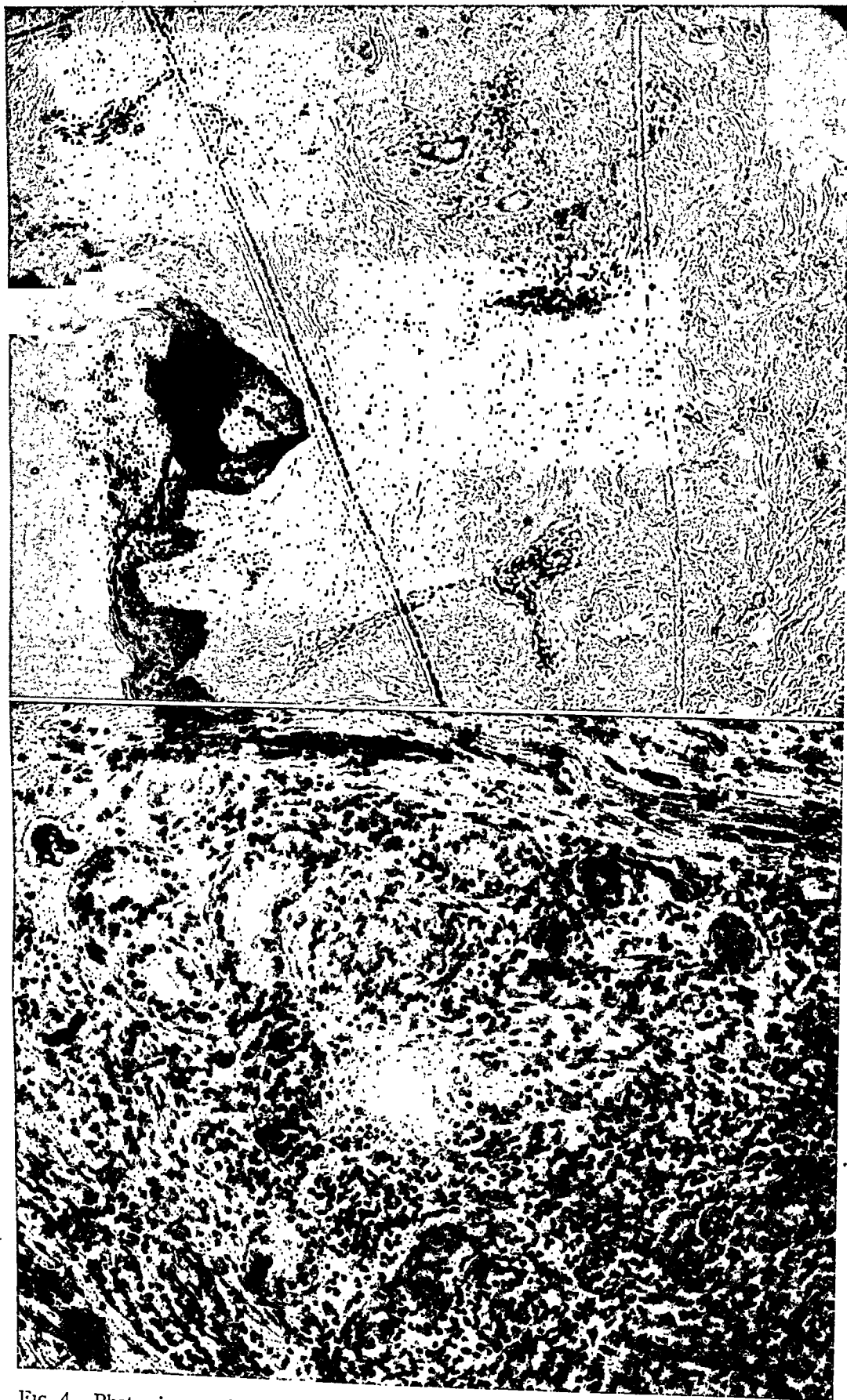


FIG. 4. Photomicrographs of the skin biopsy showing typical sarcoid infiltrations about the coiled glands, with giant and epithelioid cells surrounded by a lymphocytic reaction.

in diameter. Every nodule contains a coiled gland, but not every gland in the area has the proliferative reaction. Among the cells are lymphocytes and a few giant cells, some of which contain clear cytoplasmic vacuoles. The lining cells of the coiled glands appear normal in general, but between some of them are small lymphoid cells and in the cytoplasm of the epithelioid cells are irregular tiny acid fast globules singly or in clumps of 5 or 6." Photomicrographs of the sections are presented in figure 4.

On January 19, 1943, the blood cholesterol was 175.00 mg. per cent. The blood calcium was 10.3 mg. per cent. The blood phosphorus was 3.8 mg. per cent, and the blood phosphatase activity was 16.2 units, and 14 units on a later occasion. We are indebted to Dr. Eloise Jameson of Stanford University for performing electrophoretic studies of the serum proteins. The results on February 10, 1943, were total serum proteins 6.5 gm. per cent, albumin 3.38 gm. per cent, globulin 3.12 gm. per cent, with an A/G ratio of 1.09. The serum globulin percentages were as follows: alpha 0.56 per cent, beta total 22.16 per cent, gamma 25 per cent, and fibrinogen 0.28 per cent.

*Course.* During his stay in the hospital the patient's temperature ranged between 37.2 and 38.6° C. He had no specific complaints except for poor vision and pain in his eyes. Since his dismissal on January 19, 1943, he has been followed in the eye clinic where his vision has decreased progressively to 20/100 bilaterally. By February 11, 1943, the skin lesions had become flattened and in some cases scarred and the facial paralysis had disappeared. Except for poor eyesight, he has remained well and strong during a follow-up period of two months.

#### COMMENT

The classical features of both sarcoidosis and uveoparotid fever presented by this patient were skin nodules, adenopathy, pulmonary lesions, fever, parotitis, facial palsy, and bilateral uveitis. Failing vision and pain in the eyes were his only complaints; he did not notice the skin nodules on his forearms until they were called to his attention. It cannot be stated, therefore, whether the lesions of the skin and lungs had been present for some time, or whether they developed as part of a generalized process at the time he first noticed failing vision and facial paralysis. This young negro came recently from Tennessee to California to work in the ship yards, so that no inferences can be drawn regarding the geographical distribution of sarcoid. Although to our knowledge none has been reported, we are aware of at least one case of sarcoid and one of uveoparotid fever occurring in native Californians.

The laboratory studies were of interest. The blood count, performed during the febrile stage of the disease, was essentially normal, with no evidence of the eosinophilia or increase of mononuclear cells described in other cases. The sedimentation rate was at the upper limit of normal. The results of the electrophoretic studies of the serum proteins done four weeks after the patient's temperature had returned to normal showed the marked increase in beta, and especially in gamma, globulin reported by Fisher and Davis<sup>10</sup> as characteristic of the active stage of the disease. The serum calcium and phosphorus were normal but the phosphatase activity (alkaline) was surprisingly high in view of the absence of bone lesions found by roentgenographic examination.

## SUMMARY

A striking case is presented in which the findings of both sarcoidosis and uveoparotid fever are combined. The classical features included skin nodules, adenopathy, pulmonary lesions, fever, parotitis, facial palsy, and bilateral uveitis. This patient offers convincing evidence of the identity of the two syndromes.

## BIBLIOGRAPHY

1. BESNIER, E.: Lupus pernio de la face: synovites fungueuses (scrofulotuberculose) symétriques des extrémités supérieures, *Ann. de dermat. et syph.*, 1889, x, 333.
2. BOECK, C.: Multiple benign sarcoid of skin, *Jr. Cutan. and Genito-Urin. Dis.*, 1889, xvii, 543.
3. SCHAUAMANN, J.: Sur le lupus pernio: Mémoire présenté en Novembre 1914 a la société française de dermatologie et de syphiligraphie pour le Prix Zambaco.
4. KUZNETSKY, E., and BITTORF, A.: Boecksches Sarcoid mit Beteiligung innerer Organe, *München. med. Wchnschr.*, 1915, lxii, 1349.
5. JÜNGLING, O.: Ostitis tuberculosa multiplex cystica (eine eigenartige Form der Knochentuberculose), *Fortschr. a.d. Geb. der Röntgenstrahlen*, 1919-1921, xxvii, 375.
6. HEERFORDT, C. F.: Ueber eine Febris uveo-parotidea subchronica an der Glandula parotis und der Uvea des Auges lokalisiert und häufig mit Paresen cerebrospinalen Nerven kompliziert, *Arch. f. Ophth.*, 1909, lxx, 254.
7. BRUINS SLOT, W. J.: Besnier-Boeck's disease and uveoparotid fever (Heerfordt), *Nederl. tijdschr. v. geneesk.*, 1936, lxxx, 2859.
8. LONGCOPE, W. T., and PIERSON, J. W.: Boeck's sarcoid (sarcoidosis), *Bull. Johns Hopkins Hosp.*, 1937, lx, 223.
9. PAUTRIER, M. L.: Les lésions oculaires de la maladie de Besnier-Boeck-Schaumann (le syndrome de Heerfordt), *Arch. d'opht.*, 1938, ii, 689.
- OSTERBERG, G.: Iritis Boeck (sarkoid of Boeck in iris), *Brit. Jr. Ophth.*, 1939, xxiii, 145.
- WALSH, F. B.: Ocular importance of sarcoid: its relation to uveoparotid fever, *Arch. Ophth.*, 1939, xxi, 421.
- KING, M. J.: Ocular lesions of Boeck's sarcoid, *Trans. Am. Ophth. Soc.*, 1939, xxxvii, 422.
- LINDAU, A., and LÖWEGREN, A.: Benign lymphogranuloma (Schaumann's disease) and the eye, *Acta med. Scandinav.*, 1940, cv, 242.
10. FISHER, A. M., and DAVIS, B. D.: The serum proteins in sarcoid: electrophoretic studies, *Bull. Johns Hopkins Hosp.*, 1942, lxxi, 364.

## RUPTURE OF ABDOMINAL AORTA INTO DUODENUM (THROUGH A SINUS TRACT CREATED BY A TUBERCULOUS MESENTERIC LYMPHADENITIS)\*

By HERMAN L. FROSC, M.D., F.A.C.P., and WILLIAM HOROWITZ, M.D.,  
*New York, N. Y.*

MESENTERIC adenitis presents a difficult diagnostic problem because of its diverse symptomatology. In abdominal laparotomies mesenteric adenitis of the non-tuberculous type is found in 6 per cent of cases<sup>1</sup> whereas the tuberculous

\* Received for publication August 22, 1942.

From Dr. William A. Robert's Service at Morrisania City Hospital.

variety is discovered in 0.74 per cent. General autopsy statistics reveal tuberculous mesenteric adenitis in 1-3 per cent; in patients with tuberculosis, the condition was discovered in only 0.79 per cent.

Anatomically the abdominal lymph nodes lie along the course of the arteries especially at those points where branches arise from the abdominal aorta. The tuberculous lymph nodes may appear merely enlarged, inflamed, and discrete. They may be found in groups or masses about a central caseous node. Finally only scarred peritoneum and calcified nodes attest to a latent stage of a previous infection. Most frequently those lymph nodes are involved which drain the ileocecal region, although any nodes are susceptible to this pathologic process.

From a study of the literature Colt and Clark<sup>2</sup> found that tuberculous lymphadenitis is often a fatal disease in the very young, but in those that survive and in older persons, the disease goes on to calcification and cure. Mead<sup>1</sup> reported that 55 per cent of his series go on to a five-year cure.

It is the caseous stage of tuberculous mesenteric adenitis which is most dangerous. Rupture of a caseous node is probably fairly frequent and causes tuberculous peritonitis. Whitmore<sup>3</sup> describes a case in which a large branch of the superior mesenteric artery had been eroded by the ulcerative process of tuberculous mesenteric glands. The bowel itself showed no sign of tuberculous ulceration; the only observable lesion was the adhesive peritonitis. Fischmann,<sup>4</sup> Ruescher,<sup>5</sup> and Rawitzkaja<sup>6</sup> have each described similar cases. In Rawitzkaja's report a 14 year old girl with tuberculous spondylitis developed a spurious aneurysm of a branch of the superior mesenteric artery due to erosion caused by a tuberculous mesenteric adenitis with rupture into the subserosa of the jejunum.

The present report concerns itself with an unusual complication of tuberculous mesenteric lymphadenitis and one the exact counterpart of which we have been unable to find in the literature.

#### CASE REPORT

F. G., a 51 year old white male, station agent by occupation, was well until the age of 39 years when he was admitted to Sea View Hospital in 1928 for an osteomyelitis of the left humerus and shoulder. He remained in the hospital for 14 months, but the infection was never proved to be due to the tubercle bacillus.

Three years later, in 1931, he was a patient at Morrisania City Hospital for one month for lobar pneumonia. An electrocardiogram at this time showed a sinus tachycardia with myocardial disease.

In 1934 he was readmitted to Morrisania City Hospital with complaints of urinary retention, enlarged left testicle and a discharging sinus above the scrotum. The clinical diagnosis of tuberculous epididymitis was confirmed by microscopic examination after epididymectomy and vasectomy were done. He was discharged from the hospital as improved two months later.

During the next six years the patient was apparently well until July, 1940, when he complained of sudden epigastric pain and vomited bright red blood. Immediately following admission he vomited a pint of bright red blood. There were no other complaints and no previous history of gastric disturbance.

Examination revealed a pale, white male, appearing considerably older than 51 years, acutely ill, not restless, with no air hunger. Pulse was 100 per minute; blood pressure was 94 mm. of mercury systolic and 58 mm. diastolic. Temperature was 99° F. The heart was somewhat enlarged to the left; the apex beat was neither seen nor

felt and the heart sounds were distant and regular. The abdomen was soft, moderately distended, without tenderness. A suprapubic cystostomy scar was visible. The liver and spleen were not palpable. On the left shoulder was the scar of an osteomyelitis. A dressing over the sternum covered several draining sinuses. There was no clubbing of the fingers.



FIG. 1. Perforation in aorta.

The red blood cell count ranged from 3,000,000 to 3,200,000 and the hemoglobin from 64 to 70 per cent. Urine contained 2 plus albumin with 10 to 12 white blood cells per high power field. Blood serologic test for syphilis was negative. The Congo red test gave 38 per cent absorption. Stool was strongly positive for blood.

A clinical diagnosis of a bleeding peptic ulcer was made because of the presence of the bright red blood in the vomitus. The possibility of ruptured esophageal varices was entertained; this being secondary to cirrhosis of the liver on an amyloidosis basis as a result of the longstanding chronic infection. This was ruled out by the normal findings in the Congo red test.

However, fluoroscopic and radiographic examination of the esophagus, stomach, and duodenum showed no evidence of an organic lesion. Examination of the chest revealed a thickening of the pleura and retraction of both apices. Roentgenographic studies of the right sterno-clavicular joint and left shoulder revealed an infectious process involving the sternal end of the first rib, the inferior border of the sternal end of the right clavicle, and partial destruction of the head of the humerus and glenoid fossa.

On a Sippy régime his condition improved and he was discharged as improved one month after admission with a diagnosis of bleeding peptic ulcer. While on the ward he had had no further hematemesis.



The day following his discharge from the hospital he vomited about 500 c.c. of bright red blood and was readmitted. He appeared acutely ill, pale and cyanotic. Pulse was 100 per minute; blood pressure was 95 mm. of mercury systolic and 60 diastolic. Temperature was 97.6° F. The abdomen was soft, but tenderness was elicited in both lumbar regions. After a transfusion of 500 c.c. of citrated blood and the usual supportive measures he remained comfortable for one week. On September 5, 1940, he complained of severe stabbing epigastric pain and vomited bright red blood. He became ashen, pulseless and ceased breathing one hour later.

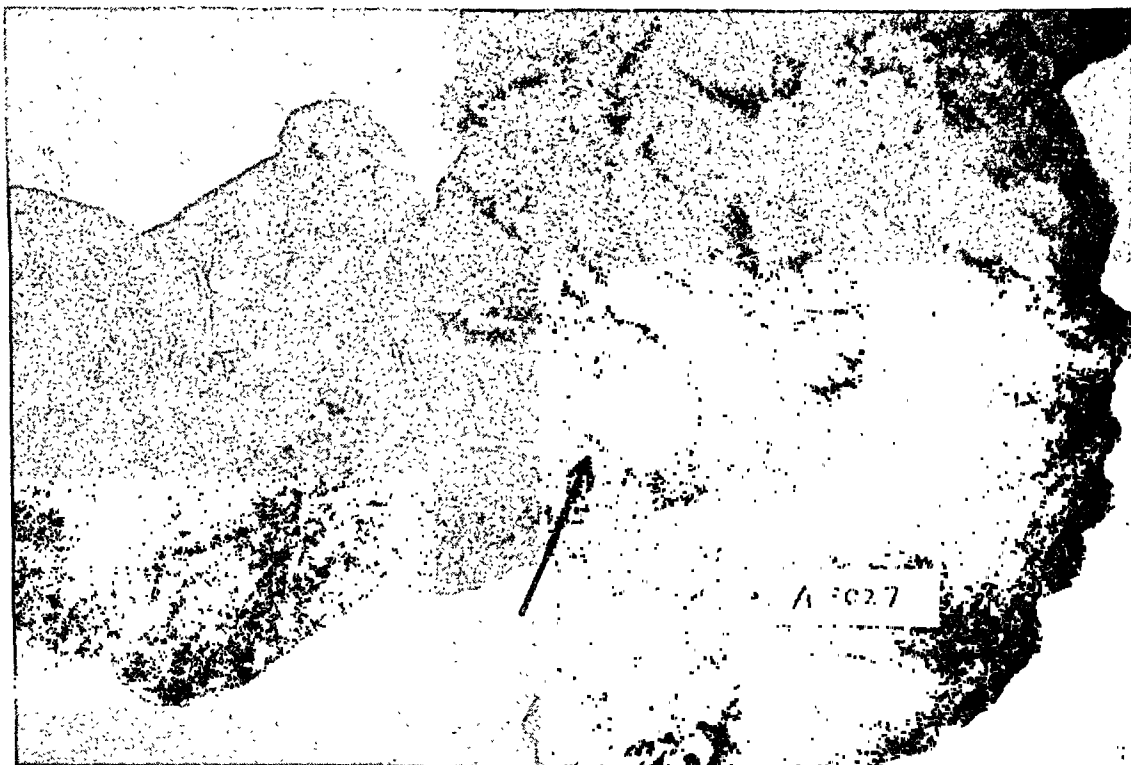


FIG. 2. Perforation in duodenum.

*Postmortem Examination.* Postmortem examination by Dr. Jacob Taub revealed fibrotic lung tissue but no evidence of caseation or tuberculosis. The abdominal viscera were extremely pale. The stomach was dilated and filled with approximately 1000 c.c. of clotted blood. The pyloric opening and duodenum were also filled with blood. In the lower third of the duodenum a punched out perforation, one-fourth of an inch in diameter and containing thrombotic material, was discovered. A probe was passed through this perforation into a sinus, one-half inch in length, communicating directly with the abdominal aorta which in this region showed extensive, ulcerative, atheromatous plaques. The communicating sinus contained a well-formed, grayish, friable thrombus. Cross-section of the abdominal aorta and duodenum in this region showed them to be separated from each other by a tuberculous lymph node, the size of a marble, through which the communicating sinus passed.

The jejunum and ileum were also filled with clotted blood. The only other significant findings were in the kidneys. The right kidney was reduced to one half normal size and contained a pasty, cheese-like material which completely filled and dilated all the calyces. The left kidney was increased in size probably because of compensatory hyperplasia. The ureters and bladder showed no gross disease.

## SUMMARY

A case of tuberculous, caseous, mesenteric lymphadenitis is presented. One large mass of caseous lymph glands had apparently eroded the abdominal aorta and formed a small opening, through which blood burrowed slowly forming a sinus tract which led to the third portion of the duodenum into which it ruptured, leading to several hemorrhages. The first two were apparently stopped by a small plug closing the opening temporarily; the last one was exsanguinating.

## BIBLIOGRAPHY

1. MEAD, CHARLES H.: Mesenteric lymphadenitis simulating acute appendicitis, *Arch. Surg.*, 1935, xxx, 492.
2. COLT, G. H., and CLARK, G. N.: Surgical aspects of diseases of abdominal glands, *Surg., Gynec., and Obst.*, 1937, lxxv, 771.
3. WHITMORE, A. T.: Note on a case of tuberculosis of the mesenteric glands with ulceration into the superior mesenteric artery, *Lancet*, 1908, ii, 157.
4. FISCHMANN, J.: Arrosion eines Astes der Arteria mesenterica superior infolge von Mesenterialdrüsentuberkulose; Verblutung, *Deutsch. Ztschr. f. Chir.*, 1931, ccxxxiii, 73.
5. RUESCHER, E.: Ein Fall von Mesenterialdrüsentuberkulose kompliziert durch Arrosion eines Mesenterialgefäßes, *Ztschr. f. Tuberk.*, 1927, xlvii, 383.
6. RAWITZKAJA, A. J.: Ein Fall von letaler Blutung also Folge einer Tuberkulose der Mesenterialdrüsen, *Beitr. z. Klin. d. Tuberk.*, 1929, lxxi, 790.
7. JUMP, H. D., and LEAMAN, W. G.: The abdominal aortic aneurysm, *Internat. Clin.*, Vol. 1; Series 2; 1939, p. 167.

## LARGE INTERAURICULAR SEPTAL DEFECT ASSOCIATED WITH TUBERCULOSIS AND AMYLOIDOSIS \*

By BENJAMIN J. ELWOOD, M.D., and ISADORE E. GERBER, M.D.,  
Jersey City, N. J.

A DEVELOPMENTAL defect of the interauricular septum may vary from a small patency of the foramen ovale to complete arrest of formation of the septum. When the interauricular communication is one or more centimeters in diameter the defect may be considered sufficiently large to permit a considerable shunt of blood from the left to the right side of the heart. As a result, there ensues a significant alteration in circulatory dynamics with consequent anatomic changes in the heart and pulmonary vessels. Modern contributions to the knowledge of interauricular septal defects have been made by Abbott,<sup>1</sup> Assman,<sup>2</sup> Roesler,<sup>3</sup> McGinn and White,<sup>4</sup> Tinney<sup>5</sup> and others so that the embryological, pathological, roentgenographic and clinical features of this lesion are now well correlated.

Although small anatomical defects of the septum are of frequent occurrence, large interauricular defects are relatively rare. This has been indicated by

\* Received for publication January 18, 1943.

From the Departments of Medicine and Pathology, Hudson County Tuberculosis Hospital, B. S. Pollak, M.D., Medical Director, Jersey City, N. J.

Roesler<sup>3</sup> who, in a most comprehensive review of the literature from 1826 to 1933, was able to collect only 62 cases in which the communication between the auricles was widely patent and not complicated by other cardiac anomalies. The following important features of large defects of the interauricular septum have been noted: (1) The hearts are always large; often they are enormous. This enlargement, even in the absence of a valvular lesion, is due entirely to dilatation and hypertrophy of the right side and is often influenced by the size of the interauricular defect. (2) The aorta is small or may be normal, whereas the pulmonary artery is always larger and together with its branches shows pronounced arteriosclerosis. (3) The densities of the enlarged pulmonary arteries and their branches have led often to an erroneous roentgen diagnosis of pulmonary tuberculosis, which in actuality occurs rarely. (4) Auricular fibrillation is common in contradistinction to other cardiovascular malformations in which auricular fibrillation is rare. (5) The clinical course leading to death is usually that of cardiac failure and the average duration of life is 36 years.

The case reported here presented a rather large defect of the interauricular septum complicated by the presence of chronic advanced pulmonary tuberculosis. The clinical course was featured by recurrent attacks of paroxysmal auricular tachycardia with cardiac decompensation, the development of advanced generalized amyloidosis, and the terminal occurrence of hypertension, uremia and pulmonary embolism.

#### CASE REPORT

C. L., a white female clerk, 21 years of age, was first admitted to the Hudson County Tuberculosis Hospital on August 29, 1932. Her family history was negative. There was nothing significant in her childhood history, and there was no knowledge of the presence of heart disease. At the age of 19 she developed a cough, several small hemoptyses, and recurrent pleurisy. She did not seek medical attention until two years later when the symptoms of fatigue, weight loss, dyspnea and cardiac palpitation on exertion appeared. A diagnosis of pulmonary tuberculosis was established and admission to the hospital followed. At this time she appeared chronically ill and moderately undernourished; her weight was 86 pounds. Examination of the thorax revealed signs of a bilateral pulmonary infiltration with excavation of the right upper lobe. There was enlargement of the heart, and a marked apical systolic thrust was visible. A coarse systolic thrill was palpable over the pulmonic area and a rough loud systolic and diastolic murmur was heard over this zone. At the apex there was a soft, blowing systolic murmur. The aortic sounds were not distinguishable. The cardiac rhythm was regular with an apical rate of 110 per minute. The peripheral pulses were small. The systolic blood pressure was 102 mm. of mercury and the diastolic 78. Cyanosis and clubbing of the fingers were not present.

A roentgenogram (figure 1) of the chest disclosed a bilateral bronchopneumonic type of infiltrate affecting principally both upper lung fields with a large area of excavation in the right upper lobe. The cardiac silhouette was large and globular with a pronounced bulge of the pulmonary conus and a small aortic arch. There was pronounced accentuation of the bronchovascular hilar markings.

Aside from the presence of tubercle bacilli in the sputum all other laboratory findings were within normal limits at this time.

The diagnosis on admission was congenital heart disease and bilateral, chronic pulmonary tuberculosis with cavitation of the right upper lobe. The nature of the cardiac abnormality was considered to be either an interauricular or interventricular septal defect, or a patent ductus arteriosus.

An attempted therapeutic pneumothorax on the right was unsuccessful because of adherent pleurae and a right temporary phrenic nerve interruption was performed in October 1932 without any effect upon the cavity. With restriction of physical activity there was roentgenographic improvement of the pulmonary lesion, and the clinical course remained uneventful for a period of two years. On July 23, 1934 she was seized suddenly with a rigor, elevation of temperature to 104° F., chills, orthopnea and prostration. On examination there was marked skin pallor and cyanosis of the

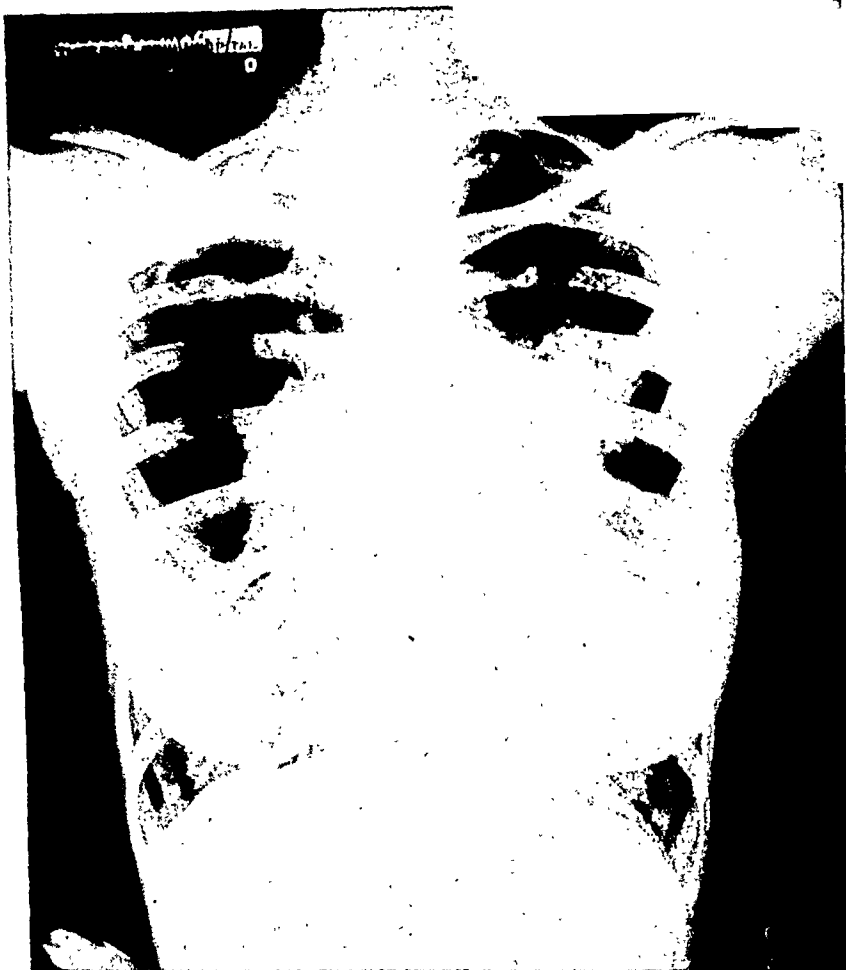


FIG. 1. Roentgenogram of chest showing the large globular heart, the small aorta, the pronounced accentuation of the pulmonary conus, the densities of the enlarged pulmonary arteries, the pulmonary changes due to the lesions of tuberculosis.

lips and nailbeds. Moist râles were heard throughout both lung fields. The heart murmurs were accentuated and the heart action was pounding; the rate was 160 per minute and the blood pressure was unchanged. Roentgenographic examination of the chest at this time revealed a marked dilatation of the heart and diffusely broadened bronchovascular hilar markings. Rapid digitalization was instituted and within 4 days the patient showed significant improvement. However, from this time on the patient was dyspneic on exertion. On a few occasions she was permitted to follow a home regimen but in the main was restricted to a semi-invalid existence in the hospital. The tuberculous involvement of the lung showed occasional mutation of the infiltration with calcification in scattered areas. There was a gradual increase in the

size of the heart as well as the pulmonary vessels and on fluoroscopy the pulsations of the latter were easily discernible well out into the fields of the parenchyma. Electrocardiograms showed extreme right axis deviation, and heart sound tracings confirmed the character of the murmurs. The patient suffered recurrent attacks of paroxysmal auricular tachycardia which were controlled with quinidine.

Albuminuria appeared during this period (1934) and thereafter persisted. The presence of amyloidosis was confirmed by the Benhold congo red test in 1936 at which time hepatomegaly and occasional slight dependent edema were demonstrable. Chemical examination of the blood revealed hypoproteinemia with reversal of the albumin-globulin ratio.

For the next five years there was persistent edema of the lower extremities with a small amount of ascites and transient facial edema. Finally in 1941 hypertension appeared for the first time; the systolic blood pressure was 154 mm. of mercury and the diastolic 100. Examination of the blood also showed for the first time elevation of the urea nitrogen. These findings were ascribed to the development of secondary contraction of the amyloid kidneys. Thereafter anasarca increased slowly. In October 1941 the patient was conscious of increasing intrathoracic discomfort. Orthopnea became more marked and the skin pallor and digital cyanosis increased. On October 6, 1941, nine years after her first admission into the hospital, she lapsed into coma and died.

*Autopsy Findings.* At postmortem examination there was marked cyanosis and some edema of the lower extremities. The abdominal cavity contained about 500 c.c. of clear, amber colored fluid. There were about 200 c.c. of similar fluid in the left pleural cavity. The pleurae on the right were adherent.



FIG. 2. Right ventricle opened to show enormous auricular and ventricular hypertrophy and dilatation. Note large interauricular septal defect.

*Heart* (figure 2). There was no excess of fluid in the pericardial cavity. The heart weighed 440 gm. There was a marked enlargement of the right ventricle which made up the entire anterior aspect of the heart. This enlargement was due to both

hypertrophy and dilatation. The left ventricle was of normal thickness and slightly dilated. The myocardium of both ventricles was firm and grayish red. There was marked enlargement of the right auricle, with pronounced hypertrophy and dilatation of the right auricular appendage. The posterior wall of the auricle was occupied by an oval orifice measuring 5 cm. in diameter. At the inferior margin of this defect there was a small ridge of tissue lying just above the site of insertion of the tricuspid valve. Laterally and superiorly the right and left auricular walls blended except for a second small fold about 3 mm. high at the site of entrance of the right pulmonary



FIG. 3. Posterior view of right lung showing enormous dilatation of pulmonary artery branches and emboli to upper lobe.

vein into the left auricle. The endocardium of the right auricle was somewhat more opaque than that of the left, thereby aiding in the demarcation of the two auricles. The leaflets of the tricuspid valve were moderately thickened, particularly along the closing margins. The trabeculae carneae of the right ventricle were thick and broad. The ostium of the pulmonary artery was enormously dilated and measured 8 cm. in circumference when opened. The pulmonary valves appeared competent. The leaflets were somewhat thickened and incipient fusion of the commissures was noted. There was enormous enlargement of the pulmonary conus. The left auricle

was small and consisted of segments of anterior and posterior wall together with the left auricular appendage. On the posterior wall there was a small thrombotic mass 2 by 3 mm. The mesial wall was formed by the defect described above; its base rested upon the superior margin of the mitral ring. The leaflets of the mitral valve were thickened and fused. The chordae tendineae were somewhat thickened and shortened. The aortic valve was competent and the cusps were translucent. The aorta was of normal size and measured 4 cm. across when opened. The coronary ostia and the lumina of the arteries were patent; the intima of the coronary arteries was smooth. The venae cavae were slightly dilated at the point of entrance into the right heart, but otherwise appeared normal.

*Lungs* (figure 3). Occupying the mid-portion of the left upper lobe there was a circular thick walled tuberculous cavity about 5 cm. in diameter. A similar cavity approximately 7 cm. in diameter was present in the right upper lobe. Scattered throughout both lungs, particularly in the upper lobes, there were many well circumscribed old and some more recent tuberculous nodules 2 to 4 mm. in diameter. There was moderate emphysema and many small calcified nodules were palpated throughout both lower lobes and to a lesser extent in the upper lobes. The main pulmonary artery and its branches were dilated to several times their normal diameter. This dilatation extended to the finest ramifications and many of the vessels were markedly thickened along their entire course. A firm grayish, somewhat adherent embolus completely occluded the lumina of the main branches to both upper lobes. Embolization was seen in some of the smaller ramifications in the lower lobes as well. The intimal surface of the main artery and its branches showed many scattered, elevated, irregular, yellowish atheromatous plaques along the entire course. The distribution of the vascular thickening was somewhat irregular. On the whole the vessels in the lower portions of the upper lobe and throughout the lower lobes were more involved. The vessels to the upper portion of the upper lobes appeared to be spared.

The liver and spleen both presented gross evidence of amyloid disease.

The kidneys were of equal size, firm, yellowish red and each weighed 115 gm. Upon stripping the capsules the surfaces showed diffuse granularity with numerous small pitted areas. On section there was some narrowing of the cortex. The cortico-medullary differentiation was not very distinct. Many of the interlobular vessels stood out prominently.

There was congo red staining of the liver, spleen and kidneys. (The last congo red test was performed seven months before death.)

The essential microscopic findings were as follows:

*Heart.* The left auricular wall showed proliferation of the subendothelial connective tissue with elastica reduplication. There were scattered partially organized thrombotic masses on the endocardial surface. These did not contain bacteria. The right ventricle showed focal areas of increased connective tissue with some atrophy of the muscle fibers. The increase in connective tissue was not limited to any specific area. There was hypertrophy of the muscle fibers throughout.

*Pulmonary Artery.* A section through the main pulmonary artery showed a mild degree of intimal proliferation. The media was not significantly altered. The elastica was intact. In the adventitia some of the vasa vasorum presented a mild periarterial infiltration of round cells.

*Lungs.* The sections through the tuberculous cavities in both upper lobes showed the characteristic appearance of old cavity with fibrosis and organization of much of the surrounding pulmonary parenchyma. The branches of the pulmonary artery presented varying degrees of dilatation, intimal proliferation and medial hypertrophy (figure 4). The larger vessels were rather markedly dilated and showed occasionally pronounced intimal proliferation with subintimal fat deposits and atrophy and scarring of the media. The smaller vessels disclosed a more pronounced degree

of intimal proliferation with elastica reduplication attended by varying degrees of narrowing of the lumina. One of the outstanding features was the rather marked variation in the distribution of the vascular alterations. The right upper lobe appeared to be the least involved and multiple sections revealed only occasional vessels with intimal proliferation and medial hypertrophy. The lower lobe showed a great degree of vascular involvement. The left lung on the other hand revealed considerable

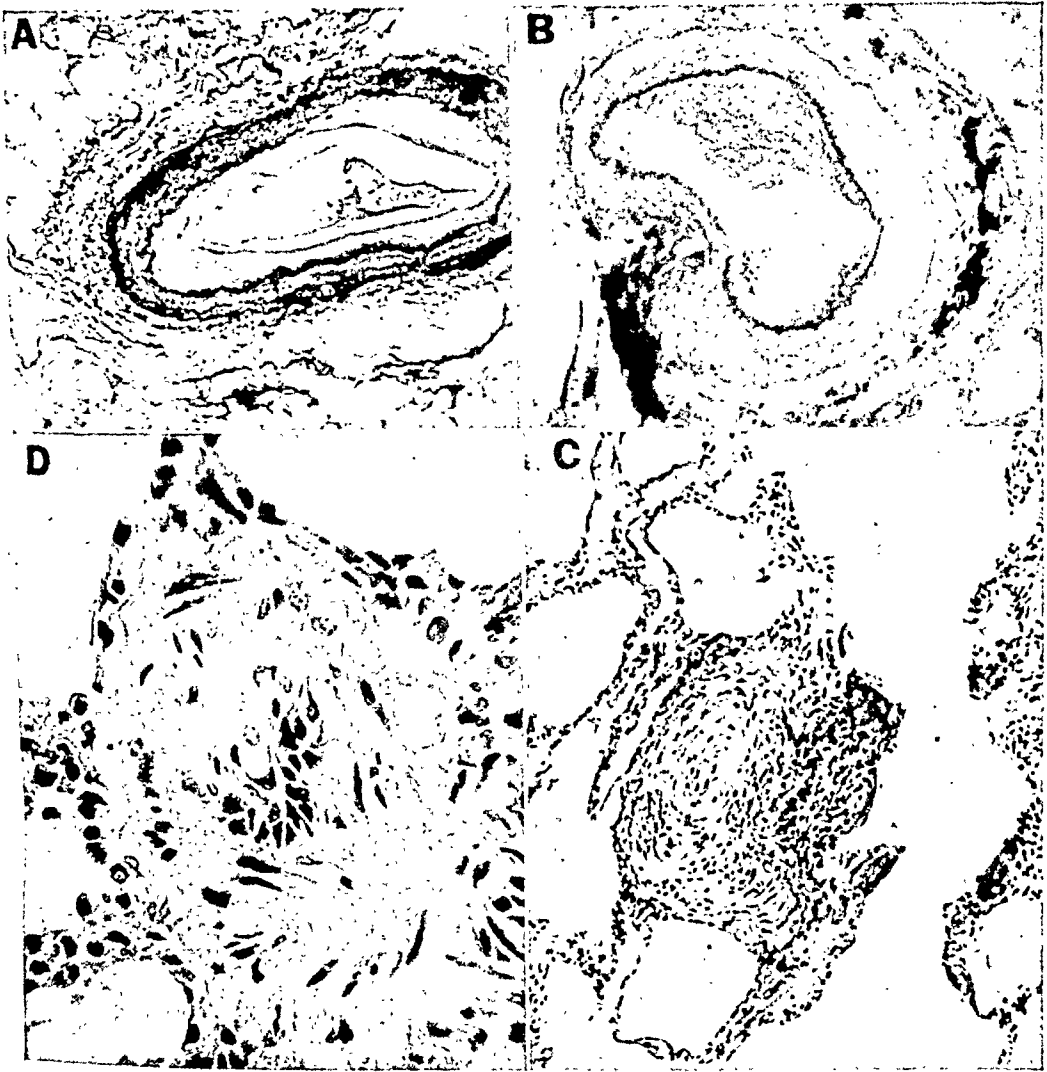


FIG. 4. *A and B*, medium sized artery branches. Elastica stain. Note intimal proliferation. *C*, low power view of arteriole showing striking medial hypertrophy with remarkable reduction in lumen. *D*, high power view of another arteriole showing similar features.

vascular changes in the upper lobe and a pronounced involvement of the smaller branches in the lower lobe. Nevertheless, even in this lung the distribution of the vascular lesions was not uniform. Very occasionally a small arteriole was seen to be filled by a partially organized thrombus.

*Kidneys.* The kidneys showed extensive amyloid infiltration involving all the glomeruli, with much scarring and glomerular and tubular atrophy. The vessels of the kidneys showed exceedingly little reaction aside from amyloid infiltration.



The liver, spleen and adrenals presented moderate amyloid infiltration. The remaining organs were without histological significance.

*Anatomical Diagnosis.* (1) Congenital heart disease: Large defect of the interauricular septum; enormous hypertrophy and dilatation of the right auricle and right ventricle. Marked dilatation of the pulmonary conus, main pulmonary artery and branches with moderate arteriosclerosis. Slight dilatation of the left ventricle. Interstitial mitral valvulitis. (2) Pulmonary embolism of both upper lobe branches. (3) Fibrocavernous tuberculosis of both upper lobes, with old and recent dissemination to all lobes. Emphysema. (4) Amyloid disease of the liver, spleen, kidneys and adrenals; amyloid contracted kidneys. (5) Anasarca.

#### COMMENT

Congenital cardiac defects provide differential diagnostic problems in which a careful evaluation of signs, symptoms and roentgenoscopic findings is essential to correct clinical impression. The roentgenoscopic evidence in this case of an enlarged globular heart with hypertrophy of the right chambers, a prominent pulmonary conus, a small aorta, and considerably widened pulsating hilar structures (pulmonary arteries) radiating into the lung parenchyma indicated a vast shunt of blood from the left to the right heart as would occur with a widely patent interauricular septal defect. Physical findings, as for example, the nature and location of the murmurs, helped to rule out a patency of the ductus arteriosus and a communication between right and left ventricles, conditions in which a somewhat similar roentgenogram is seen.

The association of advanced pulmonary tuberculosis with a large defect of the interauricular septum is rare. A chronic, intermittently active bilateral cavernous lesion was present in this case. Healing by fibrosis and calcification occurred in the infiltrate scattered throughout the lung fields, and the extensive collateral emphysema which developed undoubtedly added to the load of the right heart. The evidences of cardiac decompensation, however, were seen only in the course of the severe bouts of paroxysmal auricular tachycardia. Auricular fibrillation which is the commonly noted arrhythmia with widely patent interauricular septal defects did not occur.

The insidious development of amyloidosis which often complicates chronic cavernous pulmonary tuberculosis produced a number of important clinical changes. The appearance of dependent edema, ascites and hepatomegaly was early disproved of cardiac origin by the Benhold congo red test for amyloidosis and the existence of hypoproteinemia with reversal of the ratio of the albumin and globulin fractions. Moreover circulation time and venous pressure estimations yielded normal values. The renal contraction incident to the amyloid nephrosis further added to the burden of the heart in the appearance of hypertension. Terminal azotemia appeared as a complicating feature.

The presence of pulmonary emboli in instances of interauricular septal defect has been mentioned. It is also noteworthy that in many instances of amyloidosis pulmonary embolism is commonly encountered. Undoubtedly the latter was the factor which contributed to the occurrence of the fatal pulmonary embolism in this case.

The anatomical findings in the heart and lungs were comparable to those frequently described in instances of widely patent interauricular septal defects. One of the rather interesting and as yet unexplained features was the irregular

distribution of the pulmonary arteriosclerosis. This lesion appeared to be most extensive in the lower lobes and lower portion of the upper lobes. Even within the more involved segments of the lung the arteriosclerotic changes were not uniform. There was no distinctive relationship to the associated lesions of tuberculosis.

### CONCLUSIONS

An instance of a very large interauricular septal defect of congenital origin is described. The case was complicated by the rare presence of bilateral upper lobe cavernous tuberculosis with amyloid nephrosis and incipient renal contraction. Terminal hypertension and azotemia contributed to the decline of the patient who finally died with pulmonary embolism.

### BIBLIOGRAPHY

1. ABBOTT, M. E.: Congenital heart disease, Nelson Loose Leaf Medicine, Thomas Nelson & Sons, New York, 1929, Vol. IV.
2. ASSMAN, H.: Klinische Röntgendiagnostik der inneren Erkrankungen, Ed. IV, 1928, F. C. W. Vogel, Leipzig.
3. ROESLER, H.: Interatrial septal defect, Arch. Int. Med., 1934, liv, 339.
4. MCGINN, S., and WHITE, P. D.: Interauricular septal defect associated with mitral stenosis, Am. Heart Jr., 1933, ix, 1.
5. TINNEY, W. S., JR.: Interauricular septal defect, Arch. Int. Med., 1940, lxi, 807.

## EDITORIAL

### *CEREBRAL VASCULAR LESIONS IN RHEUMATIC FEVER*

ALTHOUGH it has long been known that rheumatic fever is a generalized infection in which many tissues and organs may be involved, the frequent occurrence of disseminated vascular lesions in this disease has not been so generally appreciated. Krehl<sup>1</sup> is generally credited as the first clearly to describe such lesions in the myocardium of patients with rheumatic valvular disease. His observations have been amply confirmed and the character of the lesions described, particularly by Karsner and Bayless and in great detail by Gross, Kugel and Epstein.<sup>2</sup> The latter observed outspoken endarteritis in one-third of their active cases.

Such lesions, however, are by no means limited to the coronary vessels. The widespread distribution of vascular lesions was emphasized by Von Glahn and Pappenheimer<sup>3</sup> in 1926. They reported finding lesions in the peripheral vessels of 10 of 47 consecutive cases of rheumatic fever. Aside from the myocardium, lesions were found in the lung, aortic valve, kidney, perirenal and periadrenal fat, ovary, testis, pancreas, appendix epiploica of the sigmoid colon and a small polyp of the cecum. To this list must be added, among others, the meninges and cerebral cortex.

The detailed histological structure of these lesions varies considerably, depending in part upon the acuteness and duration of the process. In well marked cases there is an endarteritis which, according to Von Glahn, starts with swelling, proliferation and exfoliation of the intimal endothelium, but without thrombosis. There is swelling of the vessel wall with edema and infiltration with fibrin. Peripherally he described a loose fibrillar stroma containing many nuclei, both lobulated nuclei of polymorphonuclear leukocytes and oval vesicular nuclei which tended to assume a radial arrangement about the vessel. Necrosis of cells sometimes occurred. The internal elastic lamella became swollen, shredded and broken. Later there was sometimes partial canalization by ingrowth of vascular endothelium, or the fibrin was replaced by fibrillar connective tissue, resulting in an obliterating endarteritis. The capillaries were also involved.

These changes result in local obstruction to the circulation. The tissues supplied by the diseased vessels suffer in varying degree. There may be cellular atrophy, or focal necroses, with cystic areas of softening.

Although Von Glahn<sup>3</sup> and Gross<sup>2</sup> thought the lesions were in some degree specific for rheumatic fever, subsequent investigators agree that

<sup>1</sup> KREHL, L.: Beitrag zur Pathologie der Herzklappenfehler, *Deutsch. Arch. f. klin. Med.*, 1890, xlv, 454.

<sup>2</sup> GROSS, L., KUGEL, M. A., and EPSTEIN, E. Z.: Lesions of the coronary arteries and their branches in rheumatic fever, *Am. Jr. Path.*, 1935, xi, 253.

<sup>3</sup> VON GLAHN, W. C., and PAPPENHEIMER, A. M.: Specific lesions of peripheral blood vessels in rheumatism, *Am. Jr. Path.*, 1926, ii, 235.

anatomically they can not be distinguished from endarteritis caused by other infections, and particularly not from syphilitic endarteritis.

Perhaps the first to describe such lesions in the brain were Winkelman and Eckel,<sup>4</sup> who in 1929 reported the case of a woman who developed a severe psychosis a few months after an attack of acute rheumatic fever. At autopsy shortly afterward they demonstrated a proliferative endarteritis of the small cortical vessels and minute areas of softening in the gray matter. In 1932 they described brain lesions, some of them similar in character, in five other cases.

This subject has since been studied intensively by Bruetsch,<sup>5</sup> who has recently published a summary of his observations. His attention was attracted to the subject by the fact that in routine autopsies carried out in a large psychiatric hospital, patients with rheumatic valvular disease frequently showed lesions in the brain which were regarded as rheumatic in origin. In 500 consecutive autopsies rheumatic valvular disease was present in 5 per cent of the cases. In 100 cases of schizophrenia the incidence was 9 per cent. Most of these patients had been inmates for many years, and none was known to have had rheumatic fever during his stay in the institution.

A study of about 500 cases each of male and female psychiatric patients, representing consecutive admissions to the hospital, showed that 2.6 per cent of the males and 8.1 per cent of the females either showed clinical evidence of rheumatic valvular disease or gave a history of acute rheumatic fever. It is manifestly possible that an individual with chronic rheumatic endocarditis may develop a psychosis as a result of purely psychogenic disturbances. However, in view of the fact that the incidence of rheumatic infection in the general population is generally estimated to be somewhat less than 1 per cent, these figures appear to be statistically significant, and suggest a direct relationship between the brain lesions and the psychosis in many of the cases.

Bruetsch recognizes three types of brain involvement: an obliterative endarteritis, a meningoencephalitis (rare), and cerebral embolism. The occasional occurrence of cerebral embolism in cases of mitral stenosis with auricular fibrillation, as well as in those with a complicating bacterial endocarditis has long been recognized. The endarteritic cerebral lesions are of more immediate interest. In Bruetsch's cases brain lesions were very frequent. Of the 30 cases showing rheumatic valvular disease, brain lesions were found in all but one. In 15 cases there were gross infarctions, and in 14 there were microscopic areas of softening in the cortex. Lesions in other parts of the brain were rare.

The character of the lesions in the cerebral arteries did not differ materially from those described in other organs. In most cases the patients died many years after the rheumatic infection had been established, and the

<sup>4</sup> WINKELMAN, N. W., and ECKEL, J. Z.: Endarteritis of the small cortical vessels in severe infections and toxemias, *Arch. Neurol. and Psychiat.*, 1929, xxi, 863.

<sup>5</sup> BRUETSCH, W. L.: Late cerebral sequelae of rheumatic fever, *Arch. Int. Med.*, 1944, lxxiii, 472.

cortical vessels showed largely the end stages of an obliterative endarteritis. In a few cases, however, autopsy was obtained shortly after the onset of the psychosis, and revealed early endarteritic changes with cystic areas of softening in the cortex. Even in the long standing cases, however, decades after the onset of the illness, vessels were sometimes found in which there were evidences of acute inflammation, indicating the persistence of active infection throughout this period.

The type of psychosis presented by these patients was not specific of rheumatic fever, but apparently depended upon the personality of the individual and the age at onset. In many of the younger adults it was a schizophrenia. In some of the older cases it was an involutional depression. In children it might appear as feeble-mindedness or as behavior disorders. The possible relationship of vascular changes of this type to chorea is an interesting problem which is not yet settled. Endarteritis of the cerebral vessels in chorea has been reported by von Sántha.<sup>6</sup> The fact that in chorea clinical recovery is usually complete, however, even if choreiform disturbances have been severe, suggests that the lesions are quantitatively less severe, if not qualitatively different.

Rheumatic brain disease may manifest itself clinically in other ways. Epileptiform convulsions may occur.<sup>7</sup> Foster<sup>8</sup> has pointed out that seizures of this type are several times as common in individuals with rheumatic heart disease as in the general population. One case has been reported by Alexander<sup>9</sup> with the clinical manifestations of epidemic encephalitis in which (exceptionally) the vessels of the basal ganglia were involved. A hemiplegia resulting from endarteritis of a larger vessel would be another possible manifestation.

Bruetsch's observations emphasize the fact that rheumatic fever is a protracted chronic infection, the duration of which must often be measured by years and even decades. The cerebral lesions apparently do not materially shorten life. The possibility of any significant improvement after symptoms of cerebral involvement have appeared, however, seems small, either with or without specific treatment. The most that can be hoped for is possibly to reduce the incidence and severity of such lesions by early and protracted treatment of the infection. More detailed clinical studies of these cases are needed, particularly with regard to fever, sedimentation rate and electrocardiographic changes.

<sup>6</sup> VON SÁNTHA, K.: Über Gefäßveränderungen im Zentralnervensystem bei Chorea rheumatica, *Virchow's Arch. f. path. Anat.*, 1932, cclxxxvii, 405.

<sup>7</sup> BREUTSCH, W. L.: Rheumatic epilepsy: sequel of rheumatic fever, *Am. Jr. Psychiat.*, 1942, xcvi, 727.

<sup>8</sup> FOSTER, D. B.: Association between convulsive seizures and rheumatic heart disease, *Arch. Neurol. and Psychiat.*, 1942, xlvii, 254.

<sup>9</sup> ALEXANDER, L.: The diseases of the basal ganglia, *Proc. Assoc. Research Nerv. and Ment. Dis.*, 1942, xxi, 454.

## REVIEW

*Starling's Principles of Human Physiology.* Edited and revised by C. LOVETT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. Birmingham, Jodrell Professor of Physiology in University College, London. Chapters of the special senses revised by H. Hartridge, M.A., M.D., Sc.D., F.R.S., Professor of Physiology at St. Bartholomew's Medical College. 8th edition. 1,247 pages; 24.5 × 16 cm. Lea and Febiger, Philadelphia. 1941. Price, \$10.00.

Dr. Evans has revised, rearranged, and practically rewritten the previous edition without, however, changing to any marked degree the readable style which has been a characteristic of this textbook. The point of view of the editor remains scientific rather than clinical, although clinical material of general interest has been used freely. The greatest changes have been made in the chapters pertaining to the central nervous system and the special senses. These have been completely revised to bring them in line with the newer work in these fields. Because of the extensive changes in the fields of endocrinology and reproduction, these sections have also been altered to a great extent. Although it is recognized that it is difficult to select material for a text of this kind, it would appear that somewhat more emphasis could have been put on the chapters on nutrition, particularly on vitamins and normal diet. The volume is exceptionally well illustrated. A number of the figures were drawn especially for this edition; others have been copied from the literature.

The index is very complete. Various sections of the text are followed by partial bibliographies, and specific references in the text are given in footnotes.

The editor and the publishers are to be commended for the careful preparation of this volume.

M. A. A.

## BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Heart Disease.* Third Edition. By PAUL DUDLEY WHITE, M.D. 1,025 pages; 22 × 14.5 cm. 1944. The Macmillan Company, New York City. Price, \$9.00.

*Technic of Electrotherapy and Its Physical and Physiological Basis.* By STAFFORD L. OSBORNE, M.S., Ph.D., and HAROLD J. HOLMQUEST, B.S., B.S.(M.E.) 780 pages; 23.5 × 15 cm. 1944. Charles C. Thomas, Springfield, Illinois. Price, \$7.50.

*Experimental Basis for Neurotic Behavior.* By W. HORSLEY GANTT, M.D. 211 pages; 26.5 × 18.5 cm. 1944. Paul B. Hoeber, Inc., New York City. Price, \$4.50.

*Lippincott's Quick Reference Book for Medicine and Surgery.* Twelfth Edition. By GEORGE E. REHBERGER, A.B., M.D. 1,460 pages; 27 × 18.5 cm. 1944. J. B. Lippincott Co., Philadelphia. Price, \$15.00.

*Fertility in Women.* By SAMUEL L. SIEGLER, M.D., F.A.C.S. 450 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Co., Philadelphia. Price, \$4.50.

*Fertility in Men.* By ROBERT SHERMAN HOTCHKISS, B.S., M.D. 216 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Co., Philadelphia. Price, \$3.50. (The two above-mentioned books, in slip case, \$8.00.)

*Hypertension and Hypertensive Disease.* By WILLIAM GOLDRING, M.D., and HERBERT CHASIS, M.D. 253 pages; 24 × 16 cm. 1944. The Commonwealth Fund, New York City. Price, \$3.50.

*The Argasidae of North America, Central America and Cuba.* By R. A. COOLEY and GLEN M. KOHLS. (The American Midland Naturalist. Monograph No. 1. Edited by Theodor Just.) 152 pages; 23.5 × 16 cm. 1944. University of Notre Dame, Notre Dame, Indiana. Price, \$2.00.

*Textbook of Gynecology.* 2nd Edition. By EMIL NOVAK, M.D., F.A.C.S. 708 pages; 16.5 × 24 cm. Williams and Wilkins Co., Baltimore. Price, \$8.00.

## COLLEGE NEWS NOTES

### ADDITIONAL A.C.P. MEMBERS IN THE ARMED FORCES

Previously reported in the News Notes section of this journal were the names of 1,706 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,714.

Abraham M. Balter  
Karl W. Brimmer  
William E. Kendall  
Frederick W. S. Modern

George W. Pedigo, Jr.  
Joseph G. Rushton  
Ralph F. Schneider  
Walter D. Westinghouse

Lt. Col. Charles H. A. Walton, RCAMC, F.A.C.P., who has served overseas with the Canadian Army, has received an honorable discharge, and will engage again in private practice in Winnipeg, Manitoba.

---

### NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Lt. Col. Conrad Acton, (MC), AUS, Overseas  
Dr. Robert B. Sanderson, South Bend, Ind.  
Dr. Karl Rothschild, New Brunswick, N. J.  
Dr. Harold Wentworth Stevens, Marion, Mass.

---

### GIFTS TO THE COLLEGE LIBRARY

The following gifts are gratefully accepted:

#### *Book*

Dr. James H. Hutton, F.A.C.P., Chicago, Ill.—“Endocrinology, A Brief Review for Physicians.”

#### *Reprints*

Edward L. Bortz, F.A.C.P., Captain, (MC), USNR—1 reprint.  
Glenn E. Drewyer (Associate), Lieutenant Commander, (MC), USNR—1 reprint.  
Dr. Max Millman (Associate), Springfield, Mass.—1 reprint.  
Michael Peters (Associate), Lieutenant, (MC), AUS—1 reprint.  
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—1 reprint.  
G. F. Schmitt, F.A.C.P., Lieutenant, (MC), USNR—1 reprint.  
Dr. Maurice S. Segal, F.A.C.P., Boston, Mass.—1 reprint.  
Dr. James W. Vernon, F.A.C.P., Morganton, N. C.—2 reprints.  
Dr. Salvador Zubiran, F.A.C.P., Mexico City, D. F.—“The New Hospitals of Mexico.”  
Dr. Leopoldo Herraiz Ballestero, Buenos Aires, Argentina—13 reprints.



Brown, President of Philadelphia County Medical Society. On the evening designated as "Service Night," the guest speakers will be Vice Admiral Ross T. McIntire, F.A.C.P., Surgeon General of the United States Navy, Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the United States Army, Captain Joel J. White, F.A.C.P., of the United States Navy and Dr. Charles M. Griffith, F.A.C.P., Medical Director of the United States Veterans Administration.

---

#### 7,000 WOUNDED FLOWN FROM INVASION FRONT IN THREE WEEKS BY A.A.F.

Employing new technic to save life as fast as modern war contrives to destroy, the Army Air Forces Medical Corps has pressed into service a new "flying jeep" type of airplane to rush wounded Allied soldiers from the French invasion front to hospitals removed from the scene of battle. More than 7,000 casualties were evacuated by air during the first three weeks following the Normandy invasion, according to Major General David N. W. Grant, Air Surgeon, United States Army Air Forces. General Grant further disclosed that more than 250,000 sick and wounded, American and Allied, have been carried out of battle areas by military air craft since Pearl Harbor. This number is being enlarged, all over the world, at the rate of 1,000 patients a day, he reported.

---

#### AMERICAN PEOPLE CONTRIBUTED LIBERALLY TO RUSSIAN WAR RELIEF

During the first six months of 1944, the American people have contributed \$13,715,070.99 in cash and contributions in kind to Russian War Relief, more than doubling the amount contributed in the first half of 1943, and more than three million dollars in excess of the quota set for the period covered. All supplies shipped to the Soviet Union carry a label with the American flag on it, and contributions in kind are accompanied by a personal message to the Russian recipient from the original American donor. Nearly nine and a half million dollars worth of goods have been consigned to the Soviet Union since January 1, and an additional four and a half million dollars worth is being processed and packed in Russian War Relief's two major warehouses in New York City, and Portland, Oregon, for immediate shipment.

---

#### HANDY INDEX TO HORMONE THERAPY

The Medical Research Division of the Schering Corporation, Bloomfield, N. J., will furnish free, upon request, a completely modernized version, "Handy Index to Hormone Therapy," a useful compilation of data in the hormone field, covering indications, pathogenesis, therapy, rationale and dosage.

---

#### TENTH ANNUAL MEETING, MISSISSIPPI VALLEY MEDICAL SOCIETY

The Tenth Annual Meeting of the Mississippi Valley Medical Society will be held at the Pere Marquette Hotel, Peoria, Ill., September 27-28. The program will be of a practical nature and will feature bedside medicine. Detailed program may be obtained from the Secretary, Dr. Harold Swanberg, F.A.C.P., W. C. U. Building, Quincy, Ill.

A symposium on the Heart and Circulation will be held at the Louisiana State University School of Medicine, 1542 Tulane Ave., New Orleans, October 25-27, 1944. Dr. Frank N. Wilson, F.A.C.P., Professor of Medicine at the University of Michigan Medical School, will speak on electrocardiography; Dr. Maurice Visser, of the University of Minnesota, will discuss cardiac efficiency and metabolism; Dr. Isaac Starr, of the University of Pennsylvania School of Medicine, will discuss the ballistocardiograph. Other speakers are from Tulane University and Louisiana State University. No fee will be charged; all who are interested are cordially invited to attend.

---

#### NEWS FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

Completing his work on his fifth anniversary as Chief of the Professional Service of the Office of the Surgeon General, Brigadier General Charles C. Hillman, F.A.C.P., left Washington, August 7, to take up his new position on or about August 20, as the Commanding General of the Letterman General Hospital, San Francisco. This institution, containing 2500 beds, is the principal debarkation hospital for casualties from the Pacific area. Major General Norman T. Kirk, Surgeon General of the U. S. Army, commenting on General Hillman's transfer said, in part, "General Hillman's assignment as the Commanding General of this important hospital on the West Coast illustrates the Army's concern with the care of sick and wounded soldiers. It is of paramount importance that such work be carried out under the direction of a medical man of wide experience and sound judgment. He has ably directed our Professional Service, being mainly responsible for the initiation of the blood plasma program, resulting in saving the lives of thousands of American soldiers; under his direction was organized the first x-ray examination of all Army inductees, with a lowering of the incidence of tuberculosis among military personnel to less than one-tenth that in World War I. It is a happy coincidence that the qualities of administrative ability and sound medical judgment are thus combined in one man."

General Hillman obtained his doctorate of medicine from Rush Medical College in 1911, after graduating from the University of Arkansas. Following his internship in the Cook County Hospital, Chicago, he entered the Army Medical Corps in 1912. His assignments have been largely professional in character in important medical centers of the Army. His service has included several years at tropical stations during the years of peace and inspection of medical services in overseas theaters in the current emergency. In the autumn of 1943 he visited Brazil as the official guest of the Brazilian Government; and was later decorated in recognition of the assistance that he rendered the Medical Service of the Brazilian Army.

---

Major General Norman T. Kirk, Surgeon General of the U. S. Army, returned on July 21 from visits to the Italian and Normandy battle fronts where he inspected medical facilities including those at battalion aid stations, as well as Army hospitals in England during his twenty-day trip.

With the advances of Allied forces into former enemy-held territory, the responsibility of the Army for the health of civil populations in occupied and liberated countries in both Europe and the Far East has already been and will be further increased. In meeting this responsibility, The Surgeon General is making use of the advice of outstanding civilian experts in public health. Among those recently appointed as consultants to The Surgeon General, U. S. Army, in matters pertaining to preventive medicine and public health are:

Dr. Claude E. Forkner, F.A.C.P., Director, China Medical Board. Dr. Forkner has recently returned from a year's assignment in China where he was advisor to the Committee on Medical Education of the Ministry of Education of China. While in

China, he served also as Professor of Medicine at the National Central University and the West China Union University, Chengtu, China.

Dr. George K. Strode, Director, International Health Division of the Rockefeller Foundation.

Dr. C-E. A. Winslow, Lauder Professor of Public Health, Yale University School of Medicine, and Editor, Journal of the American Public Health Association.

Dr. Ernest L. Stebbins, Commissioner of Health, New York City.

---

#### PLANS SHAPED FOR ARMY MEDICAL HISTORY

Representatives of the professional and administrative services of the Office of the Surgeon General, met July 26, 1944, to discuss plans and to make progress reports on the medical history of the war. Colonel Albert G. Love, who was a member of the editorial staff that published the history of the Medical Department of the United States Army in World War I, has been directing the work since August, 1941 on the history of the present war. Marked progress is being made in assembling information from medical installations in this country and overseas. Editors have been selected for the volumes on the medical specialties and the administrative phases of the medical service. In addition to the research and editorial work to be done in the Office of the Surgeon General, historical activities will be carried forward by officers assigned to headquarters of overseas theaters. They will secure first-hand reports of the over-all medical services, particularly those rendered under combat conditions including evacuation of the wounded, the flow of supplies, and other problems. Officers in overseas theaters who have had extensive experience with medical and surgical problems peculiar to this war are being asked to record their observations for the history.

Medical histories were published by the Office of the Surgeon General following the Civil War and World War I. The volumes have done much to perpetuate and disseminate professional, administrative and organizational medical advances developed under the impetus of war. British authorities are carrying forward a similar plan.

---

#### MASON GENERAL HOSPITAL DEDICATED

Surgeon General Norman T. Kirk dedicated the Mason General Hospital, Brentwood, Long Island, New York, June 22, 1944. A special school for training medical officers in neuropsychiatry has been located at this institution. Colonel Cleve C. Odom, F.A.C.P., is the Commanding Officer of the hospital.

---

#### COLONEL WAKEMAN HONORED POSTHUMOUSLY

Colonel Frank B. Wakeman, F.A.C.P., was awarded the Legion of Merit posthumously for his meritorious work in connection with the training program of the Army Medical Department. The citation reads—

"For exceptionally meritorious conduct in the performance of outstanding services from July, 1940, to March, 1944. Colonel Wakeman, with rare foresight, initiative, and organizing ability, laid the groundwork for the necessary expansion in all phases of Medical Department training, placing in operation replacement training centers, service schools for officers, Medical Department Enlisted Technicians Schools, and an Officer Candidate School, long before the entry of the United States into the

war. As a result of his insight into medical requirements and the execution of plans, the Medical Department was able to expand greatly its training activities following December 7, 1941, and also, because of training already given, to render an efficient medical service to the Army during the very rapid expansion that followed the declaration of war. Colonel Wakeman's unusual foresight, aggressive execution of approved plans, and selfless devotion to the best interests of the Army and the Medical Department are in the highest traditions of the service."

Colonel Wakeman was awarded the Henry Welcome Prize in 1938 for his thesis on an immunizing antigen of the typhoid bacillus. He died in March of 1944 of a coronary occlusion while attending a conference at Fort Monmouth, N. J.

---

#### COLONEL FLICKINGER RETURNS FROM BURMA

Colonel Don Flickinger (Associate), formerly Wing Surgeon of the A.A.F. Air Transport Command, India-China wing, recently returned to the United States for a new assignment. Colonel Flickinger, it will be remembered, parachuted into the Burma jungle in August, 1943, to bring aid to the victims of a plane crash. He brings glowing reports of the volume and success of air evacuation of casualties from the China-Burma fighting front.

Colonel Flickinger was awarded the Legion of Merit for working upon methods of sighting pilots forced down at sea. He also holds the Distinguished Flying Cross, Soldier's Air Medal and a Presidential unit citation.

---

Major William O. Benenson (Associate), formerly of Napanoch, N. Y., has been advanced to Chief of the Medical Service of the ASF Regional Hospital, Fort Benning, Ga., and Captain Michael Peters (Associate), formerly of Telford, Pa., has been advanced to the Assistant Chief of the Medical Service of the same hospital.

---

Major William J. Mitchell (Associate), formerly of Alhambra, Calif., has been named Commanding Officer of the Station Hospital at Fort Douglas, Utah.

---

Dr. Harold R. Carter (Associate), Denver, Colo., addressed the Larimer Medical Society, Berthoud, Colo., June 6, 1944, on "Present Day Trends in the Diagnosis and Treatment of the Psychoneuroses."

---

Dr. Paul F. Whitaker, F.A.C.P., Governor for North Carolina, was installed as President of the Medical Society of the State of North Carolina at the annual meeting at Pinehurst, N. C., May 1. Dr. William H. Smith, Goldsboro, N. C., was elected Vice-President.

---

Lt. Col. Thomas Fitz-Hugh, Jr., F.A.C.P., formerly of Philadelphia, was promoted to the grade of Colonel on July 25, 1944.

---

Dr. Louis H. Bauer, Hempstead, N. Y., has been elected a member of the Board of Trustees of the American Medical Association.

---

Colonel Garfield G. Duncan, F.A.C.P., formerly Associate Professor of Medicine, Jefferson Medical College, and Chief of the Medical Service of the Pennsylvania Hospital, Philadelphia, has been awarded the Legion of Merit by command of General MacArthur for his work on malarial control and atabrine studies.

Dr. William Earl Clark, F.A.C.P., and Dr. William M. Ballinger, F.A.C.P., are President-Elect and First Vice President, respectively, of the Medical Society of the District of Columbia.

---

Dr. Edward Sterling Nichol, F.A.C.P., Miami, has been elected President of the American Therapeutic Society, and Dr. Oscar B. Hunter, F.A.C.P., Washington, has been elected Secretary.

---

Dr. R. D. Thompson, F.A.C.P., Medical Director of the State Tuberculosis Sanatorium, Orlando, Fla., has been elected President of the Southern Conference on Tuberculosis.

---

Dr. William H. Gillentine, F.A.C.P., has been made President-Elect of the New Orleans Graduate Medical Assembly for 1944-1945.

---

Dr. J. W. Finch, F.A.C.P., Hobart, Okla., was recently appointed Chairman of Procurement and Assignment of Kiowa County.

---

Dr. S. E. Thompson, F.A.C.P., Kerrville, Dr. Robert G. McCorkle, F.A.C.P., San Antonio, and Dr. H. F. Carman, F.A.C.P., Dallas, have been elected President, First Vice President and Second Vice President, respectively, of the Texas Chapter, American College of Chest Physicians.

---

Dr. E. V. DePew, F.A.C.P., San Antonio, Tex., has succeeded Dr. H. J. Schattenberg, F.A.C.P., as a member of the San Antonio Board of Health. Dr. Schattenberg resigned to resume his place as Consultant to the State Board of Health.

---

Dr. R. Finley Gayle, F.A.C.P., Richmond, was recently elected a member of the National Committee for Mental Hygiene.

---

Dr. John T. O'Mara, F.A.C.P., Baltimore, has been reelected Secretary-Treasurer of the Board of Medical Examiners of Maryland.

---

Dr. Rollin H. Stevens, F.A.C.P., Detroit, is President of the Detroit Institute of Cancer Research, which was established in 1941. The Institute has purchased from the Detroit Edison Company the Detroit Edison Club property, will remodel the two buildings as a temporary cancer research laboratory and hopes to coöperate closely in cancer research with the proposed Medical Science Center of Wayne University.

---

Dr. Alexander H. Stewart, F.A.C.P., Harrisburg, Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, and Dr. William H. Perkins, F.A.C.P., Philadelphia, were speakers on the program of a conference on health and human relations held under the auspices of the Pennsylvania Department of Health at State College, Pa., July 18-19. The program dealt chiefly with sex education.

---

Dr. John F. Kenney, F.A.C.P., Pawtucket, has been made President-Elect of the Rhode Island Medical Society. Dr. Elihu S. Wing, F.A.C.P., Providence, is the present incumbent.

Dr. Chester S. Keefer, F.A.C.P., Boston, has been appointed the Medical Administrative Officer of the Committee on Medical Research. Several new divisions have been established. Dr. E. Cowles Andrus, F.A.C.P., Baltimore, is Chief of the Division of Medicine, and Dr. Joseph T. Wearn, F.A.C.P., Cleveland, is Chief of the Division of Physiology. The headquarters office in Washington, D. C., is at 2101 Constitution Ave., N. W.

---

Dr. Roy L. Leak, F.A.C.P., recently resigned as Superintendent of the Connecticut State Hospital, Middletown, after holding the position since April, 1922.

---

Dr. Theodore G. Klumpp, F.A.C.P., President of the Winthrop Chemical Company, has announced the establishment of a division of product development which will explore the post-war commercial potentialities of products being supplied by this Company to the Armed Forces as well as new products developed in the Company's laboratories.

Dr. Klumpp is also Chairman of the Advisory Committee of Physicians on Drug Exhibits of the New York Academy of Medicine. The Academy has set up plans for a continuous non-commercial drug exhibit at its headquarters. An adequately qualified person will be in charge to answer questions and explain new drugs. Pamphlets and literature will be furnished, giving the research and clinical usage and describing the products.

---

Dr. Tasker Howard, F.A.C.P., after being connected with the Long Island College of Medicine for some 34 years, has retired as Professor and Executive Officer of the Department of Medicine.

Dr. William Dock, Professor of Medicine at the University of Southern California, Los Angeles, has accepted the position, on a full-time basis, at the Long Island College of Medicine.

---

Dr. Alexander M. Burgess, F.A.C.P., Providence, R. I., has been appointed Professor of Health and Hygiene in a newly created department of medical science at Brown University. The new department is intended to assist the University in assuming a larger responsibility for the general education of its students in matters of health.

---

Dr. Roy L. Sexton (Associate), Washington, D. C., is a member of a three-man medical mission sent to the Pribilof Islands in the Bering Sea to assist local medical personnel in the examination of 400 Aleut natives, recently repatriated after two years in southeastern Alaska.

---

The Chicago Medical Society has been sponsoring a series of popular health talks, given at the Museum of Science and Industry, Chicago. The first lecture, "Facts about Cancer," was delivered by Dr. Josiah J. Moore, F.A.C.P., President of the Chicago Medical Society and Treasurer of the American Medical Association. Dr. Samuel M. Feinberg, F.A.C.P., gave the lecture on August 2, "Allergy, Facts and Fiction"; Dr. James H. Hutton, F.A.C.P., August 9, "Your Glands and What They Do to and for You"; and Dr. Andrew C. Ivy, F.A.C.P., August 23, "Aviation Medicine."

Dr. Oliver Perry Kimball, F.A.C.P., Cleveland, and Dr. Margaret Bell, F.A.C.P., Ann Arbor, were among physicians cited by the University of Chicago on June 10 as "useful citizens." Dr. Kimball was largely responsible for the collection of funds from Cleveland alumni to establish a local scholarship at the University, and Dr. Bell is Professor of Hygiene and Physical Education, Chairman of the Physical Education for Women and physician in the Health Service of the University of Michigan.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered an address on "The Contribution of Psychiatry to Democratic Morale," at the 100th anniversary of the Butler Hospital, Providence, R. I., May 10. This is the oldest hospital in the State.

Brigadier General John M. Willis, F.A.C.P., Surgeon of the 9th Service Command, U. S. Army, Fort Douglas, Utah, addressed the Utah State Medical Association's annual meeting at Salt Lake City, August 25-26, on "Administration and Hospitalization in a Service Command." Lt. Col. Lauren H. Smith, F.A.C.P., addressed the same meeting on "Treatment in War Psychiatry."

Dr. Richard H. Freyberg (Associate), heretofore Assistant Professor of Internal Medicine at the University of Michigan Medical School, Ann Arbor, has accepted an appointment as Chief of the Department of Medicine and Pediatrics at the Hospital of Special Surgery, New York City, effective September 1, 1944.

Dr. Floyd L. Rogers, F.A.C.P., Lincoln, Nebraska, is President of the Nebraska State Medical Association. Dr. William J. Reeder (Associate), Cedar Rapids, is a Vice President.

Dr. E. Roland Snader, Jr., F.A.C.P., Philadelphia, was elected to the Council of the American Diabetes Association at the recent June meeting in Chicago. Dr. Edward S. Dillon, F.A.C.P., Philadelphia, was elected Second Vice President at the same meeting.

#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 1 (Maine, New Hampshire, Vermont, Massachusetts)—Dr. C. S. Keefer, Chairman; Dr. M. C. Sosman, Dr. A. W. Allen.

REGION No. 2 (Connecticut, Rhode Island)—Dr. S. B. Weld, Chairman; Dr. C. Barker, Dr. A. M. Burgess.

*Station Hospital, Dow Field, Bangor, Maine*

September 21 Burns and Reconstruction Surgery

*Dispensary, U. S. Naval Air Station, Brunswick, Maine*

September 21 The Psychoneuroses and Their Management

*Station Hospital, Fort Williams, Portland, Maine*

September 21 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation—  
Drs. Samuel H. Proger and T. Duckett Jones

*Station Hospital, Presque Isle, Maine*

September 21 The Use of Penicillin and the Sulfa Drugs—Dr. Charles A. Janeway

*Dispensary, U. S. Naval Construction Training Center, Quoddy Village, Maine*

- September 21 The Pneumonias and Other Respiratory Infections—Dr. Cutting B. Favour

*Station Hospital, Grenier Field, Manchester, New Hampshire*

- September 20 Acute Abdominal Emergencies

*U. S. Naval Hospital, Portsmouth, New Hampshire*

- September 21 Chest and Abdominal Injuries

*Station Hospital, Fort Banks, Boston, Massachusetts*

- September 21 The Skin—Dr. Francis M. Thurmon

*U. S. Naval Hospital, Chelsea, Massachusetts*

- September 21 Acute Infections of the Central Nervous System—Dr. Derek E. Denny-Brown

*Station Hospital, Fort Devens, Massachusetts*

- September 21 Stomach, Biliary Tract, Intestinal Disorders—Drs. J. Howard Means, Robert R. Linton and Laurence L. Robbins

*Station Hospital, Camp Edwards, Massachusetts*

- September 21 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

*Cushing General Hospital, Framingham, Massachusetts*

- September 21 Peripheral Vascular Disease—Dr. E. Everett O'Neil

*Station Hospital, Camp Myles Standish, Taunton, Massachusetts*

- September 21 Contagious Diseases and Complications—Dr. Edwin H. Place

*U. S. Marine Hospital, Brighton, Massachusetts*

- September 21 Blood Dyscrasias and Transfusions—Dr. Louis K. Diamond

*Station Hospital, Westover Field, Chicopee Falls, Massachusetts*

- September 21 Pilonidal Sinus and Common Diseases of the Anus and Rectum—Dr. E. Parker Hayden

*Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island*

- September 21 Diarrheal Diseases—Drs. Ralph E. Wheeler and Francis C. McDonald

*U. S. Naval Hospital, Newport, Rhode Island*

- September 21 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation—Drs. Paul D. White and Mandel E. Cohen

*Station Hospital, Bradley Field, Windsor Locks, Connecticut*

- September 21 Joint Injuries—Dr. John H. T. Sweet, Jr. and associates

*Air Corps Station Hospital, New Haven, Connecticut*

- September 21 Fractures of Extremities—Dr. Frank S. Jones



*Station Hospital, Fort H. G. Wright, Fishers Island, New York*

September 21 Head, Spine and Nerve Injuries

REGION No. 10 (Kentucky, Tennessee)—Dr. E. L. Henderson, Chairman; Dr. C. W. Dowden, Dr. H. H. Shoulders.

*Combined War-Time Graduate Medical Meeting and Kentucky State Medical Association Meeting, Lexington, Kentucky*

- September 19 Chemotherapeutics in Pediatrics—Dr. John A. Toomey  
 Chemotherapy (Penicillin)  
 Civilian Medical Essayist—Dr. Donald G. Anderson  
 Symposium (Military Essayists)  
 Medical Aspects—Brigadier General Hugh Morgan  
 Surgical Aspects—Colonel B. N. Carter  
 Venereal Disease Treatment—Lieutenant Colonel Thomas Sternberg  
 Oration in Medicine—Dr. Frederick G. Speidel  
 Psychosomatic Medicine—Dr. Maurice Levine  
 Industrial Health Hazards—Colonel Anthony Lanza  
 Current Problems in Aviation Medicine—Major General David N. W. Grant  
 The Present Status of Pain Relief in Labor—Dr. Frederick H. Falls  
 Cardiovascular Diseases—Dr. William D. Stroud  
 (Evening Program)  
 President's Address—Dr. Oscar O. Miller  
 Accelerated Medicine Today and Tomorrow—Dr. Roger I. Lee  
 Address—Dr. Edward Henry Cary
- September 20 Symposium on Tropical Diseases  
 Epidemiology—Dr. R. E. Dyer  
 Medical Aspects of Tropical Diseases—Captain Alphonse McMahon  
 The New Weapons for Control of Insect-borne Diseases—  
 Brigadier General James S. Simmons  
 The Surgical Aspects of the Chronic Dyspepsias—Dr. Irvin Abell  
 Oration in Surgery—Dr. J. Farra Van Meter  
 Arthritis—Dr. Ralph Pemberton  
 Address—Brigadier General Fred W. Rankin  
 Nutrition—Its Relation to Deficiency Diseases—Colonel John D. Youmans

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole.

*Mayo General Hospital, Galesburg, Illinois*

- September 20 Diseases of the Kidneys, Uro-genital Tract  
 Diseases of the Kidneys—Edema  
 Surgical Considerations
- October 4 Blood Dyscrasias  
 Acute and Chronic

*Camp Ellis, Illinois*

- September 20 Conditions Affecting Glucose Metabolism  
 Endocrine—Pituitary—Thyroid—Adrenal—Pancreatic  
 Renal, Alimentary, Hepatic. Diff. Diagnosis and Treatment

- October 4      Orthopedic Problems of General Interest  
                     Low Back Pain—Foot and Knee Strain—March Fracture, etc.

*Camp McCoy, Wisconsin*

- September 20   Diseases of the Intestinal Tract  
                     Regional Ileitis, Colitis, Diverticulitis.    Diagnosis and Treatment.  
                     Dysentery—Army and Bacillary  
                     Malignancies

- October 4      Symposium on Organic Neurology  
                     Central and Peripheral

*Camp Grant, Illinois*

- September 20   Dermatological Diseases  
                     Clinic with Presentation of Cases and Slides.    Diagnosis and  
    Treatment  
                     The Less Common Venereal Diseases  
    Lymphogranuloma Venereum, Granuloma Inguinale,  
    Chancroid, Yaws

- October 4      Psychiatry—Psychoneuroses—Neurocirculatory    Asthenia—Malingering, etc.

*Truax Field, Wisconsin*

- September 20   Malignancies in the Army Age Group  
                     Melanomata  
                     Teratomata  
                     Lymphoblastomata

- October 4      Endocrinology  
                     Addison's Disease, Adrenal Cortex in Shock, Parathyroid Tetany,  
                     Traumatic Hypogonadism, Hypothyroidism, Hyperthyroidism,  
                     Post-Traumatic Pituitary Syndrosis

*Chanute Field, Rantoul, Illinois*

- September 20   Chemotherapy—Present Status  
                     Sulfonamides  
                     Penicillin  
                     Gramicidin

- October 4      Gall Bladder and Liver Disease  
                     Mechanism of Liver Function  
    Diagnosis and Medical Treatment of Liver and Gall Bladder  
    Disease  
                     Surgical Pathology and Treatment

(The names of those speakers which do not appear on the above schedule are to be announced.)

## AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION

FRANCIS M. RACKEMANN, M.D., *Secretary*

263 Beacon Street, Boston 16, Mass

August 11, 1944

TO THE MEMBERS OF THE COUNCIL:

## In re: The Next Meeting

Our President, Dr. C. Sidney Burwell, and I have been considering the matter carefully, and we submit to you our thoughts with the request that you send us your approval and/or your comments in the near future.

Last May in Atlantic City, several members discussed the next meeting informally and decided to postpone decision "until we could see how the war was going." The war is going well but it is not won—our troubles are not yet over and they are not likely to be over for many months to come. All our young members are in Service and as for the older members it is most impressive to see the important positions which they hold and the heavy responsibilities which they carry. Whereas many men would try hard to come to a meeting, the trip would entail a large effort and the men would not stay long. Incidentally, transportation is still difficult and still restricted.

To us, therefore, it seems wisest to postpone the meeting for one more year and to hope that in October 1945 we can have the most interesting, the biggest and the best meeting which the "Climatological" has ever held. What do you say?

With kind regards,

Yours sincerely

FRANCIS M. RACKEMANN  
*Secretary pro tem*

---

LIEUT. COLONEL MARTIN A. COMPTON

## APPOINTED TO SURGEON GENERAL BOARD

Lieut. Colonel Martin A. Compton, M.C., has been appointed as a member of a board of the Office of The Surgeon General, the purpose of which is to prepare, develop and implement the medical portion of the War Department's program for aid to civilian populations in liberated countries. This board was established in June, 1943.

Colonel Compton was born in Palmyra, Illinois, in 1913, attended Bradley Polytechnic Institute and Washington University School of Medicine (St. Louis) and received his medical degree from the Washington University School of Medicine (St. Louis). In 1938 he was appointed First Lieutenant in the Medical Corps and attained a Captaincy two years later. In 1942 he was promoted to the grade of Major and became Lieut. Colonel in the Fall of 1943.

Colonel Martin A. Compton has been associated with and Chief of the Requirements Branch in the Office of The Surgeon General since 1941.

---

LIEUT. COLONEL ROBERT JAMES WILSON, M.C., DIES

The War Department has announced the death of Lieut. Colonel Robert James Wilson, M.C., staff officer of the United States Army Bruns General Hospital, Santa Fe, New Mexico, which occurred on July 11. Grave-side services were held at Arlington Cemetery July 20; he was accorded a military funeral.

Colonel Wilson was born in 1906 in Buffalo. After completing his work at the Kentucky Military Institute he obtained the Bachelor of Arts degree at the University of Maryland in 1927. The University of Buffalo awarded him the degree of Doctor of Medicine in 1931. He received his commission as First Lieutenant in the Medical Corps in June of that year, serving internship at the Walter Reed General Hospital; there he served as assistant chief ward officer in the surgical service. Upon completing this work, he was assigned to the Army and Navy General Hospital at Hot Springs, Arkansas.

He became associated with the Office of The Surgeon General Finance and Supply Division in 1941. Shortly thereafter he was appointed Chief of the Civilian Personnel Division—the position which he held until his assignment to the Bruns General Hospital in 1942.

---

#### ARMY INCREASES OFFICER CANDIDATE QUOTAS FOR MEDICAL ADMINISTRATIVE CORPS

An increase in quotas for admission to officer candidate courses leading to commissions in the Medical Administrative Corps of the Army has been announced by the War Department.

Quotas which until recently have been extremely limited have been revised to permit acceptance of 2,000 men within the next eight weeks for 17-week courses. The primary reason for the increase is the need for more officers qualified for administrative duties in the Army Medical Department to free members of the Medical Corps for professional duties.

In recent months only the Medical Administration Corps Officer Candidate School at Camp Barkeley, Texas, has been accepting candidates. Under the new plan, the Officer Candidate School at Carlisle Barracks, Pennsylvania, was re-opened on June 24.

---

#### THE AUGUST ARMY MEDICAL BULLETIN

The following articles appeared in the August issue of the *Army Medical Bulletin*:

Laboratory Aids in Diagnosis of Rocky Mountain Spotted Fever

Colonel Harry Plotz, M.C.

1st. Lieut. Kenneth Wertman, Sn.C.

Captain Reginald L. Reagan, Sn.C.

Plaster of Paris Casts and Splints

Captain J. Vernon Luck, M.C.

Medical Service in the New Georgia Campaign

Nomogram for Computing Morbidity and Mortality Rates

Anesthesia in the Combat Zone

Captain Gerald Shorts, M.C.

Cutaneous Leishmaniasis

Major David Ball, M.C.

Captain Raymond C. Ryan, M.C.

Oral Rehabilitation

Captain R. C. Reichert, D.C.

Herniated Nucleus Pulposus

Major Robert C. L. Robertson, M.C.

Captain William G. Peacher, M.C.

Surgical Problems in the Buna Campaign

Colonel Augustus Thorndike, M.C.

Vaccinia Occurring at Short Intervals

Captain Carl A. Minning, M.C.

Inspection of Fish of the Pacific Northwest

Captain Ernest W. Bloomquist, V.C.

The Diagnosis of Dengue

Major George V. LeRoy, M.C.

Captain Howard A. Lindberg, M.C.

Experimental Use of Penicillin in Treatment  
of Sulfonamide-Resistant Gonorrhea

Captain Robert J. Murphy, M.C.

Modified Orthopedic Table Constructed in the Field

Captain Victor Mayer, M.C.

Psychoses in the Army

Major Norman Q. Brill, M.C.

Captain Edmund F. Walker, M.C.

Rocky Mountain Spotted Fever

Major Oscar A. Palatucci, M.C.

Major Bruno A. Marangoni, M.C.

---

#### CLINICAL PSYCHOLOGISTS AID ARMY

Clinical Psychologists commissioned in the Adjutant General's Department are being made available for assignment to the Office of The Surgeon General for the neuropsychiatric sections of named and numbered general and station hospitals of 1,000 beds or more, the War Department announced on July 1, 1944. Requisitions for such officers will be forwarded to the Adjutant General through commanding generals of service commands concerned, or theater commanders when applicable.

Clinical psychologists will be assigned to duty in the neuropsychiatric sections of the hospital to serve under the direction and supervision of the chief of the neuropsychiatric section. Their duties will be to—

a. Aid in the development and administration of the program of counseling designed to prepare convalescent patients for return to military service.

b. Assist in the preparation of clinical records, particularly including those requiring the use and interpretation of special psychological tests as desired by the chief of the neuropsychiatric section.

c. Assist in studies of special psychological problems related to the classification and retraining of neuropsychiatric casualties.

d. Assist in the determination of the appropriate military occupational specialty of men who are designated as ready for assignment, and to advise regarding their assignment to a specific duty or special training.

e. Perform such other professional and administrative duties in the hospital as will best assist the neuropsychiatrist in the accomplishment of the best management and disposition of patients.

---

#### POSTWAR TRAINING OF MEDICAL CORPS OFFICERS

The Office of The Surgeon General has announced the appointment of a committee to formulate plans for postwar training of Medical Corps Officers who will be separated from the military service at the end of the war. The committee consists of: Brig. General Raymond W. Bliss, Chief of Operations Service—*Chairman*; Brig. General James S. Simmons, Chief of Preventive Medicine Service; Colonel James R. Hudnall, Chief of Personnel Service; Brig. General Fred W. Rankin, Director of Surgery Division; Brig. General Hugh J. Morgan, Director of Medicine Division; Colonel Floyd L. Wergeland, Director of Training Division; Colonel Wil-

liam P. Holbrook, M.C. and Lieut. Colonel R. H. Meiling, M.C., representatives from the Army Air Forces; Colonel R. B. Skinner, M.C. representative from the Army Ground Forces; George B. Darling, M.D., representative from the National Research Council.

---

#### GEORGE M. POWELL PROMOTED

Colonel George M. Powell, M.C., director of the Special Planning Division, Operations Service in the Office of the Surgeon General, advanced from the grade of Lieut. Colonel on June 15. He was born in Los Animas, Colorado, in 1906 and graduated from the Colorado College in 1927. He obtained his medical degree from the Washington University School of Medicine in St. Louis, Missouri. In 1939 he completed nine months of training in Internal Medicine at the Walter Reed General Hospital.

Colonel Powell served as Cardiologist and later became Chief of the Medical Service at Gorgas Hospital, Ancon, Canal Zone, where he was stationed from the Fall of 1939 to the Fall of 1942. Then he was assigned to the Medical Replacement Center of Camp Joseph T. Robinson in Arkansas, where he performed the duties of Assistant Regional Commander until he became full Regional Commander in 1943.

---

#### DECORATIONS FOR SCRUB TYPHUS CONTROL SERVICE

The Bronze Star Medal has been awarded to an officer of the Sanitary Corps and seven enlisted men of the Medical Department for their services in the prevention of scrub typhus on Goodenough Island in the South Pacific as announced on May 16, 1944 by the Sixth Army Headquarters.

Although these men were fully aware of the danger of contracting scrub typhus, they voluntarily applied themselves to the task of preparing camp sites in order to bring about the rapid and complete control of this disease on Goodenough Island. Their services were rendered during the periods December 27, 1943 to February 7, 1944 and March 13-22, 1944.

---

#### U. S. ARMY BLIND CENTERS

The Army Medical Department has designated two hospitals, namely, Valley Forge General Hospital, Phoenixville, Pa., and Dibble General Hospital, Menlo Park, California as blind centers where all blinded casualties are being sent to receive a preliminary course in social rehabilitation while undergoing any necessary medical or surgical treatment.

On July 21 the first group of blinded casualties was received at Old Farms Convalescent Hospital (Special), Avon, Conn., which has been designated as the blind center where the final phase of social rehabilitation is given. This group has undergone the preliminary training at Valley Forge General hospital, and during their stay at Old Farms will receive more advanced training in social rehabilitation prior to discharge from the Army and transfer to the Veterans Administration.

---

Major Alexander Pierce Ormond, F.A.C.P. (MC), AUS, Chief of Medical Service of the Station Hospital, Reno Army Air Base, Reno, Nevada and formerly of Akron, Ohio, gave an address before the Nevada Branch of the American Social Hygiene Association in Reno on July 12, 1944. He spoke on "The Army's Venereal Disease Control Program." Dr. Lawrence Parsons, F.A.C.P., president, introduced the speaker.

## GOVERNOR BRICKER COMMENTS ON AMERICAN MEDICINE

Governor John W. Bricker of Ohio, Republican Vice Presidential candidate, in addressing the Creve Coeur Club at Peoria last February 22 said, among other things, "The American doctors have made eminent progress in caring for the health of our people. Medical organizations and private hospital groups are making substantial progress toward the goal of providing adequate medical and hospital care for all. In view of this record I regard the proposals emanating from this administration for governmental intervention between the doctor and his patient as an undeserved affront to a loyal and admirable profession, and a distinct threat for the future health of our people. It is these meddlesome activities in so many spheres that properly belong to the states or to the people themselves that have led to the multiplicity of government agencies which are unsupervised and uncontrolled, and which it is impossible to supervise or control. Please do not misunderstand me. Government must be responsive to the needs of social progress in every field. It must continue to be. Human welfare means more than good intentions and material help. It must promote education, health and public welfare. But it must leave to individual human beings a full measure of control over their own destiny. Governmental management and regimentation invariably lead to national chaos and disorder."

## OBITUARIES

## DR. KENNON DUNHAM

Dr. Kennon Dunham, F.A.C.P., Cincinnati, Ohio, died April 27, 1944, of coronary thrombosis; aged 72.

Dr. Dunham was born in Fairfield, Ohio, in 1872, and received his medical degree from Miami Medical College, now the University of Cincinnati College of Medicine, 1894. He later did postgraduate work at Johns Hopkins University School of Medicine, the University of Wisconsin Medical School, in London and in Germany. For many years he was Associate Professor of Medicine and Head of the Department of Tuberculosis at the University of Cincinnati College of Medicine and the Cincinnati General Hospital. At one time he was Attending Physician to the Cincinnati Tuberculosis Sanatorium, and during World War I he served in the Medical Corps of the U. S. Army as Chief of the Laboratory Service at Oteen, N. C.

Dr. Dunham was a former President, 1921, of the Cincinnati Academy of Medicine, a member of the Ohio State Medical Society, the American Roentgen Ray Society, the American Clinical and Climatological Association, the National Tuberculosis Association, Society of Thoracic Surgery, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1923. He was the author of many published papers, and a physician who will be sorely missed.

## DR. GEORGE McCLINTOCK HUTCHISON

Dr. George McClintock Hutchison, F.A.C.P., Ridgway, Pa., died January 6, 1944, of peritonitis; aged 68.

Dr. Hutchison was born in Brockway, Jefferson County, Pa., November 18, 1875. In 1900 he graduated from the Pennsylvania College of Dental Surgery with the degree of D.D.S., and in 1907 from the Medico-Chirurgical College of Philadelphia with the degree of M.D. In 1927 he completed the course at the University of Pennsylvania Graduate School of Medicine, receiving the degree of Master of Medical Science.

For many years Dr. Hutchison was a practicing physician at Dagus Mines and Kersey, Pa. For the last several years he practiced internal medicine at Ridgway. He was a member of the Staff of the Elk County General Hospital and a Visiting Physician to the Andrew Kaul Memorial Hospital at St. Marys. He was a member of the Elk County Medical Society, the Pennsylvania State Medical Society, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1936.

## DR. ANGUS MacKAY

Dr. Angus MacKay, M.B., F.A.C.P., Toronto, Ont., Canada, died March 4, 1944, from an acute attack of coronary thrombosis; aged 54.



Dr. MacKay was born in the Township of West Zorra, County of Oxford, and was a direct descendant of the Sutherland MacKays who were pioneers of that section of Ontario. His early education was attained in Embro and the Collegiate Institute of Woodstock. He received his Bachelor of Medicine degree from the University of Toronto in 1916. From that date until 1919, he served with the rank of Captain in the Royal Canadian Army in Canada, England and France. He interned at St. Michael's Hospital and assisted Dr. David Smith, of Stratford, for a time before entering practice in Toronto. He did postgraduate work in New York and in Rochester, Minn.

As a classmate and friend of the late Sir Frederick Banting, F.A.C.P., he was one of the first to study the clinical application of insulin, and was soon recognized as an authority on its use in the treatment of diabetes. He limited his practice to Internal Medicine, and was made a Fellow of the American College of Physicians in 1931.

In the Toronto Western Hospital he had charge of the diabetic patients, but he was a favorite consultant also in other departments of the hospital. His marked common sense and his clinical acumen won the confidence of his colleagues, and his loss is a major calamity to the staff.

Dr. MacKay made valuable contributions to the literature of diabetes and hypertension; he wrote book reviews with discrimination; he served for years on the Publication Committee of the Toronto Academy of Medicine, was a member of its Council from 1938 to 1941 and Chairman of the Section of Pathology, 1930-31, and of the Section of Medicine, 1940-41. His hobbies were fishing, gardening, golf and the reading of historical novels and biographies. He is survived by his wife, Mrs. Edna Catherine Hanna MacKay, a son, Ross Cameron and a daughter, Elizabeth Ann.

—Taken in part from the Bulletin of the  
Toronto Academy of Medicine

### DR. HOMER WOOLERY

Dr. Homer Woolery (Associate) of Bloomington, Ind., died April 22, at the age of 71 of coronary thrombosis.

Dr. Woolery was born December 24, 1872; received his A.B. degree in 1897 in Indiana University, and his M.D. in 1907 from the same institution. He later pursued postgraduate study at Harvard Medical School. He practiced the specialties of internal medicine and pediatrics in Bloomington for a great many years. He was a member of the Phi Delta Theta and Nu Sigma Nu Fraternities, also a member of the Monroe County Medical Society, the Indiana State Medical Society, the Central States Pediatric Society and the American Academy of Pediatrics. He had been an Associate of the American College of Physicians since 1921 by virtue of former membership in the American Congress on Internal Medicine.

Dr. Woolery was well liked by his fellow practitioners and was well known to the Indiana University student body over a period of many years, for he was a friend to all of them.

ROBERT M. MOORE, M.D., F.A.C.P.,  
Governor for Indiana

### DR. CHARLES HARTWELL COCKE

Dr. Charles Hartwell Cocke, First Vice-President of The American College of Physicians, died of coronary occlusion on the morning of August 3, 1944. Stricken on July 29, he realized that his illness would probably be fatal and, with his customary thoughtfulness and consideration, he furnished his secretary, Miss Studebaker, with a list of names to be notified in case of his death. Dr. Paul H. Ringer, his physician and devoted friend of thirty-three years standing, was with him at the end.

Dr. Cocke was born in Columbus, Miss., on December 1, 1881, the son of Charles Hartwell Cocke, who was the second President of the Industrial Institute and College, now known as Mississippi College for Women, and Rowena Lockart Hudson Cocke. He received his early education at Episcopal High School, where he was an honor student and leader in school activities. From there he went to the University of Virginia where he graduated with an A.B. degree in 1902. He received his M.D. degree from Cornell University Medical College in 1905, and in 1908 he did postgraduate study at the Allgemeines Krankenhaus, Vienna, and the hospitals of London and Paris. In 1914 he married Miss Amy Grace Plank, of Carlisle, Pa. Their home life was ideal and they lived happily through the years. Mrs. Cocke was with her husband at the end. Many is the visitor who has enjoyed the cordial hospitality of this gracious couple in their home.

Going to Asheville, North Carolina, by reason of impaired health, he remained to become one of that city's most illustrious, useful and respected citizens. He was for many years Attending Physician for the Asheville Mission and Biltmore Hospitals. He was Consulting Physician to the Learline Reaves Sanatorium (Greenville, Tenn.) and Patton Memorial Hospital, Hendersonville, North Carolina. He was co-founder and medical director of the Zephyr Hill Sanatorium, and consultant to most of the hospitals of Asheville.

Dr. Cocke was a Diplomate of the American Board of Internal Medicine; President, 1923, Buncombe County Medical Society; Vice-President, 1927, Medical Society of the State of North Carolina; Vice-President, 1932, Southern Medical Association; Vice-President, 1934, American Clinical and Climatological Association; Vice-President, 1935 and 1936, American College of Chest Physicians; Member of National Tuberculosis Association, Southern Interurban Clinical Club, American Association of the History of Medicine, American Heart Association; Fellow, American Medical Asso-

ciation; Member of the Phi Kappa Psi and Nu Sigma Nu fraternities, and, during World War I, he was Chief Consultant and Secretary of his local Medical Advisory Board.

The Medical Society which he enjoyed and loved most was The American College of Physicians. He became a Fellow of the College in 1928 and was elected to the Board of Governors, representing the State of North Carolina, in 1929. He was Chairman of the Board of Governors from 1925 to 1942 and became Vice-President of the College in 1942; was re-elected in 1944 and held that office at the time of his death. He served on



CHARLES HARTWELL COCKE, ASHEVILLE, N. C.

REGENT, AND CHAIRMAN, BOARD OF GOVERNORS

numerous committees of the College; he was a member of the Committee on Credentials for many years and on this Committee he performed signal service in connection with the standards of the College. Dr. Cocke loved the College and everything about it and maintained an abiding interest in its welfare and progress. To him, more than any other man, goes the credit for the fine and healthy growth of the College in his adopted State of North Carolina. Giving his enthusiastic support and his recognized talent to the promotion of its welfare from 1928 on, it can be truthfully said that his passing has lost for the College one of its most loyal and valuable members.

Dr. Cocke was author of numerous publications in the best medical journals in the country. Throughout his professional life there were very few years that he did not make at least one contribution to medical literature.

Although medicine was his primary interest, Dr. Cocke, being the good citizen that he was, gave liberally of his time and talent to the civic and church affairs of his home city, Asheville. For years he was a member of the Asheville Chamber of Commerce, serving as Vice-President in 1939 and Director from 1938 to 1940. He served on the Board of Directors of the Asheville Community Chest for three years. A member of the Trinity Episcopal Church, he served as vestryman for twenty years, was a former Senior Warden, Trustee of the Diocese and a member of the Standing Committee of the Diocese for many years. He also served as President of the Men's Bible Class of his church.

The family, the friends, the community in which he lived, his patients and the organizations to which he belonged will sorely miss this scholarly, friendly and talented man. Splendidly trained, possessed of a keen intellect and having the utmost regard for the nobility of his calling, it is not strange that he was respected throughout his State and section as an outstanding physician. Patients were drawn from great distance by his well deserved reputation.

A man of many social graces and broad intellectual interests, he touched the lives of many people. Those of us who knew him were benefited by the warmth and glow of his character. It is hard to believe that we will not again hear the cheery greeting and receive the warm handclasp of this dynamic, scholarly and sincere man. His patients loved him, his family loved him; and his friends loved him! His memory will ever remain graven on our hearts.

PAUL F. WHITAKER, M.D., F.A.C.P.,  
Member of Board of Governors for North Carolina

## POSTGRADUATE COURSES, AUTUMN, 1944

### THE AMERICAN COLLEGE OF PHYSICIANS

The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. The Advisory Committee on Postgraduate Courses will plan other courses during the winter and spring of 1945. Because of conditions due to the War, the program cannot be planned a long time in advance, but the College will attempt to provide an adequate program of postgraduate study to serve those members of the College who will find it convenient and possible to pursue refresher courses.

The courses are organized especially for Fellow and Associates of the College, but where facilities are available, they will be open to non-members with adequate preliminary training, preference to be given to non-members in the following order: (1) candidates for membership; (2) Medical Officers in the Armed Forces; (3) physicians preparing for examinations by their certifying boards; (4) other non-members having adequate background for advanced work. By direction of the Board of Regents, registrations from non-members of the College may not be accepted more than three weeks in advance of the opening of any course.

The courses are made available by the College to its members at minimum cost, because the College assumes full responsibility for promotion, advertising, printing and registration.

**FEES**—\$20.00 per week to members of the College; \$40.00 per week to non-members; Medical Officers of the Armed Forces of the United States and Canada, free. At least one-half of the registration fee shall be paid at time of filing application; the balance shall be paid not later than one week in advance of the opening of any course. Note that in the case of Course No. 3 a special, all-inclusive rate for tuition, room and board will apply: namely, \$50.00 for members; \$70.00 for non-members; \$30.00 for Service physicians.

The advance payment may be refunded by the College to any registrant who for adequate reason is unable to pursue the course, providing notice of withdrawal is registered ten days in advance of the opening of the course.

**REGISTRATION**—All registrations should be filed directly with the Executive Offices of the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. An official registration form, copy of which can be procured from the Executive Offices, must be used. Registrations will be assigned in order of receipt.

The College will record all registrations with the respective institutions offering the courses. Therefore, no registration should be made except through the American College of Physicians. A matriculation card will be sent to each registrant when his fee has been paid in full.

#### COURSE NO. 1—CARDIOLOGY

(October 2-7, 1944)

MASSACHUSETTS GENERAL HOSPITAL

Boston, Mass.

PAUL D. WHITE, M.D., F.A.C.P., *Director*

(Minimal Registration, 30; Maximal Registration, 50)

The full details of this course have already been published in the August issue of the *ANNALS OF INTERNAL MEDICINE*, and, therefore, are not hereunder repeated.

## COURSE NO. 2—GENERAL MEDICINE

(October 9-14, 1944)

UNIVERSITY OF OREGON MEDICAL SCHOOL

Portland, Ore.

HOMER P. RUSH, M.D., F.A.C.P., *Director*

(Minimal Registration, 25; Maximal Registration, 60)

## OFFICERS OF INSTRUCTION

*Guests*

Captain Ercell A. Addington, MC, Barnes Hospital.  
Major Noyes L. Avery, Jr., MC, Barnes Hospital.  
Colonel Charles K. Berle, MC, F.A.C.P., Barnes Hospital.  
Major Frederick J. Bradshaw, Jr., MC, Barnes Hospital.  
Commander L. T. Coggeshall, MC, USNR, Marine Bks., Klamath Falls.  
Captain William W. Waddell, MC, Barnes Hospital.

David W. E. Baird, M.D., F.A.C.P., Dean, University of Oregon Medical School.  
William Y. Burton, M.D., Assistant Professor of Radiology.  
T. Homer Coffen, M.D., F.A.C.P., Clinical Professor of Medicine.  
William S. Conklin, M.D., Assistant Professor of Medicine.  
Norman A. David, M.D., Professor of Pharmacology.  
Knox H. Finley, M.D., Associate Professor of Psychiatry.  
John H. Fitzgibbon, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.  
Wesley E. Gatewood, M.D., Assistant Clinical Professor of Medicine.  
Morton J. Goodman, M.D., Assistant Clinical Professor of Medicine.  
John R. Hand, M.D., Assistant Clinical Professor of Urology.  
Hance F. Haney, M.D., Professor of Physiology.  
Blair Holcomb, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.  
Warren C. Hunter, M.D., Professor of Pathology.  
Selma Hyman, M.D., Assistant Professor of Radiology.  
Ralph C. Matson, M.D., F.A.C.P., Associate Clinical Professor of Medicine.  
Sidney Mayer, Jr., M.D., Clinical Associate in Medicine.  
John D. McGovern, M.D., Assistant Professor of Pathology.  
Frank R. Menne, M.D., F.A.C.P., Professor of Pathology.  
John R. Montague, M.D., Clinical Associate in Medicine.  
Frank R. Mount, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.  
Edwin E. Osgood, M.D., F.A.C.P., Associate Professor of Medicine.  
Dorwin L. Palmer, M.D., Assistant Clinical Professor of Radiology.  
Matthew C. Riddle, M.D., Associate Professor of Medicine.  
Homer P. Rush, M.D., F.A.C.P., Associate Clinical Professor of Medicine.  
Laurence Selling, M.D., F.A.C.P., Professor of Medicine.  
James T. Speros, M.D., Assistant Professor of Medicine.  
Kenneth C. Swan, M.D., Assistant Professor of Ophthalmology.  
Wilbur R. Todd, M.D., Assistant Professor of Biochemistry.  
Ben Vidgoff, M.D., Clinical Instructor in Medicine.  
Charles C. Wilson, M.D., Clinical Associate in Medicine.  
Ivan M. Woolley, M.D., Clinical Associate in Radiology.

## OUTLINE OF COURSE

Monday, October 9.

A.M. Session

- 8:00- 8:50 Registration, Introduction and Instructions.  
Drs. Baird, Rush and Selling.
- 9:00- 9:50 X-Ray Interpretation of Diseases within the Thorax.  
Drs. Palmer, Burton, Hyman and Woolley.
- 10:00-10:50 Chemotherapy: Penicillin.  
Dr. Osgood.
- 11:00-11:50 Recent Advances in Cardiology.  
Dr. Coffen.

P.M. Session

- 1:00- 2:50 Clinical Conference.  
Dr. Selling.
- 3:00- 3:50 The Scope of Tropical Medicine: its subject content.  
Dr. Riddle.
- 4:00- 4:50 The Psychic Factors in Asthma.  
Dr. Mayer.
- 5:00- 5:50 Puberty Praecox and Associated Syndromes.  
Dr. Hand.

Tuesday, October 10.

A.M. Session

- 8:00- 8:50 Clinical Pathological Conference.  
Drs. Hunter, Menne and McGovern.
- 9:00- 9:50 X-Ray Interpretation of Diseases of the Gastrointestinal Tract.  
Drs. Palmer, Burton, Hyman and Woolley.
- 10:00-10:50 Chemotherapy: The Sulphanilamides.  
Dr. Osgood.
- 11:00-11:50 The Combination Use of Insulins.  
Dr. Holcomb.

P.M. Session

- 1:00- 1:50 Functional Heart Disturbances: The Tension State.  
Dr. Selling.
- 2:00- 2:50 Electroencephalograph.  
Dr. Finley.
- 3:00- 3:50 The Scope of Tropical Medicine: The Biological and Sociological Factors.  
Dr. Riddle.
- 4:00- 4:50 The Importance of Eye Ground Examination in Internal Medicine.  
Dr. Goodman.
- 5:00- 5:50 The Eye and Diabetes.  
Dr. Swan.

Wednesday, October 11.

A.M. Session

- 8:00- 8:50 Clinical Pathological Conference.  
Drs. Hunter, Menne and McGovern.
- 9:00- 9:50 X-Ray Interpretation of Diseases of the Bones.  
Drs. Palmer, Burton, Hyman and Woolley.

10:00-10:50 Chemotherapy: The Arsenicals.

Dr. Osgood.

11:00-11:50 The Value and Interpretation of Gastroscopic Examinations.

Dr. Fitzgibbon.

#### P.M. Session

1:00- 2:50 Clinical Conference.

Dr. Rush.

3:00- 3:50 Useful Diagnostic Procedures in Tropical Medicine.

Dr. Riddle.

4:00- 4:50 The Present Status of Estrogenic Therapy.

Dr. Vidgoff.

5:00- 5:50 Arthritis; a Workable Classification.

Dr. Wilson.

Thursday, October 12.

#### A.M. Session

8:00- 8:50 Clinical Pathological Conference.

Drs. Hunter, Menne and McGovern.

9:00- 9:50 X-Ray Interpretation of Diseases of the Genito-urinary Tract.

Drs. Burton, Palmer, Hyman and Woolley.

10:00-10:50 The Present Status of Thyroid Depressing Drugs.

Dr. David.

11:00-11:50 Clinical Experience with Thiouracil (Deracil Lederle).

Drs. Wilson and Montague.

P.M. Session will be spent at Barnes General Hospital. The Army program has been arranged by Colonel Charles K. Berle, MC, Commanding.

1:00- 1:45 Certain Problems when Tropical Diseases are moved to the Temperate Zone.

Commander Coggeshall.

1:45- 2:30 Physiology of Chest Leads.

Major Avery.

2:30- 3:15 Reconditioning, both Mental and Physical, as practiced at this Hospital, with Special Consideration of War Neuroses.

Major Bradshaw.

3:15- 4:00 Bronchogenic Carcinoma.

Captain Addington.

4:00- 4:45 Some Points in Diagnosis of Amoebic Hepatitis with Illustrative Cases.

Captain Waddell.

After these papers, an opportunity will be given the attending doctors to visit the Hospital.

Friday, October 13.

#### A.M. Session

8:00- 8:50 Clinical Pathological Conference.

Drs. Hunter, Menne and McGovern.

9:00- 9:50 Irradiation Therapy.

Drs. Palmer, Burton, Hyman and Woolley.

10:00-10:50 Present Status of the Physiological Background of the Vitamins.

Dr. Todd.

11:00-11:50 The Present Status of the Physiological Mechanism of Hypertension.

Dr. Haney.



## P.M. Session

- 1:00- 2:50 Clinical Conference.  
Dr. Gatewood.
- 3:00- 3:50 Experiences in War Medical Problems.  
Lt. Col. Mount.
- 4:00- 4:50 The Present Status of Androgen Therapy.  
Dr. Vidgoff.
- 5:00- 5:50 Arthritis; Plans of Therapy.  
Dr. Wilson.

Saturday, October 14.

## A.M. Session

- 8:00-12:00 Clinical Conference: Chest Diseases.  
Drs. Matson, Conklin and Speros.

---

COURSE NO. 3—INTERNAL MEDICINE

(October 9-14, 1944)

CENTER FOR CONTINUATION STUDY,

UNIVERSITY OF MINNESOTA

Minneapolis, Minn.

JULIUS M. NOLTE, *Director*

*Center for Continuation Study*

WILLIAM A. O'BRIEN, M.D., *Director,*

*Postgraduate Medical Education*

CECIL J. WATSON, M.D., F.A.C.P., *Head,*

*Department of Medicine*

EDWARD H. RYNÉARSON, M.D., F.A.C.P.

*Associate Professor of Medicine,*

*Mayo Foundation, Rochester*

(Minimal Registration, 30; Maximal Registration, 50)

OFFICERS OF INSTRUCTION

- George N. Aagaard, Jr., M.D., Instructor in Medicine, Medical School.
- John M. Adams, M.D., Assistant Professor of Pediatrics, Medical School.
- Wallace D. Armstrong, M.D., Professor of Physiological Chemistry, Medical School.
- Elexious T. Bell, M.D., Professor of Pathology, Medical School.
- Clarence Dennis, M.D., Associate Professor of Surgery, Medical School.
- Charles A. Evans, M.D., Assistant Professor of Bacteriology, Medical School.
- Gerald T. Evans, M.D., Associate Professor of Medicine, Medical School.
- Edmund B. Flink, M.D., Associate Professor of Medicine, Medical School.
- Malcolm M. Hargraves, M.D., Instructor in Medicine, Mayo Foundation, Rochester.
- Wallace E. Herrell, M.D., F.A.C.P., Assistant Professor of Medicine, Mayo Foundation, Rochester.

- Horton C. Hinshaw, M.D., F.A.C.P., Assistant Professor of Medicine, Mayo Foundation, Rochester.
- Frederick W. Hoffbauer, M.D., Associate Professor of Medicine, Medical School.
- Max H. Hoffman, M.D., Clinical Assistant Professor of Medicine, Medical School.
- F. Raymond Keating, Jr., M.D., Instructor in Medicine, Mayo Foundation, Rochester.
- Edwin J. Kepler, M.D., F.A.C.P., Associate Professor of Medicine, Mayo Foundation, Rochester.
- Bernard G. Lannin, M.D., Clinical Instructor in Surgery, Medical School.
- Thomas Lowry, M.D., Clinical Assistant Professor of Medicine, Medical School.
- Irvine McQuarrie, M.D., Professor of Pediatrics, Medical School.
- J. Arthur Myers, M.D., F.A.C.P., Professor of Preventive Medicine and Public Health, Medical School.
- Julius M. Nolte, Director, Center for Continuation Study, University of Minnesota.
- William A. O'Brien, M.D., Director, Postgraduate Medical Education, University of Minnesota.
- E. R. Rickard, M.D., Director, Influenza Research Laboratory, Minnesota State Department of Health, Minneapolis.
- Leo G. Rigler, M.D., Professor of Radiology, Medical School.
- Edward H. Ryneanson, M.D., F.A.C.P., Associate Professor of Medicine, Mayo Foundation, Rochester.
- Thomas H. Seldon, M.D., Instructor in Anesthesia, Mayo Foundation, Rochester.
- Morse J. Shapiro, M.D., Clinical Associate Professor of Medicine, Medical School.
- Wesley W. Spink, M.D., F.A.C.P., Associate Professor of Medicine, Medical School.
- Richard L. Varco, M.D., Assistant Professor of Surgery, Medical School.
- Owen H. Wangenstein, M.D., F.A.C.S., Professor of Surgery, Medical School.
- Cecil J. Watson, M.D., F.A.C.P., Professor of Medicine, Medical School.

The purpose of this course is to review certain phases of internal medicine. It will be presented by representatives from the faculty of the Medical School, Minneapolis, and the Mayo Foundation, Rochester, Minn. The program will consist of lectures, clinics, round tables, clinical dialogues, conferences, discussions, demonstrations and motion pictures. The group will live in the Center for Continuation Study Building, where lectures will be given. Clinics and Conferences will be held in the University of Minnesota Hospitals on the campus. The medical library is located just a short distance from the Center for Continuation Study. Arrangements have been made to house a maximum of fifty physicians. Twenty single rooms with detached bath and fifteen double rooms with adjoining bath have been made available. Occupants of double rooms may designate the physician who is to occupy the room with them, or they will be assigned a roommate pending final approval. All meals will be served in the dining room of the building. Members of the military service on active duty will be charged only for their room and meals. The advantage of living together during the week cannot be overemphasized, as it eliminates transportation difficulties and provides ample time for group discussion.

#### OUTLINE OF COURSE

Monday October 9.

7:30

Breakfast.

8:30

Orientation.

Center for Continuation Study Program.

Mr. Nolte.

Continuation Course in Internal Medicine.

Drs. O'Brien and Watson.

Laboratory Methods used in the Study of Blood Diseases.

Dr. Flink.

Interpretation of the Peripheral Blood Count.

Dr. Hargraves.

Fundamental Aspects of the Anemias.

Dr. Watson.

12:30

Luncheon.

2:00

Diagnosis and Treatment of the Anemias.

Dr. Watson.

Transfusions with Blood and Blood Plasma.

Dr. Seldon.

Transfusion Reactions.

Dr. Flink.

6:30

Dinner.

Tuesday, October 10.

7:30

Breakfast.

8:30

Characteristics of Virus Disease Agents.

Dr. Evans.

Influenza.

Dr. Rickard.

Virus Respiratory Infections in Infancy and Childhood.

Dr. Adams.

Virus Pneumonias.

Dr. Spink.

12:30

Luncheon.

2:00

Case Finding in Tuberculosis.

Dr. Myers.

Chemotherapy of Tuberculosis.

Dr. Hinshaw.

Clinical Radiologic Dialogue—Respiratory Infections.

Drs. Spink and Rigler.

6:30

Dinner.

Wednesday, October 11.

7:30

Breakfast.

8:30

Clinical Conference—Penicillin Therapy.

Drs. Spink and Herrell.

Clinical Pathologic Conference.

Drs. Watson, Bell and Associates.

12:30

Luncheon.

2:00

Changes in Blood Electrolytes in Disease.

Dr. Kepler.

Disease of the Adrenals.

Dr. McQuarrie.

Disturbances of the Pituitary Gland.

Dr. Rynearson.

6:30

Group Dinner—Faculty and Course Members.

Thursday, October 12.

7:30

Breakfast.

8:30

Calcium, Phosphorus and Phosphatase Studies.

Dr. Armstrong.

Hyperparathyroidism.

Dr. Keating.

The Male Sex Hormones.

Dr. Hoffman.

Thiouracil Therapy:

Dr. Evans.

12:30

Luncheon.

2:00

Fundamental Aspects of Jaundice.

Dr. Watson.

Liver Biopsy and Liver Function.

Dr. Hoffbauer.

Diagnosis and Treatment of Jaundice.

Dr. Watson.

6:30

Dinner.

Friday, October 13.

7:30

Breakfast.

8:30

Medical-Surgical Problems:

Treatment of Gastric and Duodenal Ulcer.

Dr. Lamm.

Treatment of Ulcerative Colitis.

Dr. Dennis.

Preparation of Surgical Patients.

Dr. Varco.

Treatment of Tumors of the Bowel.

Dr. Wangenstein.

12:30

Luncheon.

2:00

Differential Diagnosis of Coronary Occlusion and Myocardial Infarction.

Dr. Aagaard.

Treatment of Congenital Heart Disease.

Dr. Shapiro.

Clinical Radiologic Dialogue—Bronchial Obstruction.

Drs. Lowry and Rigler.

6:30

Dinner.

Saturday, October 14.

7:30

Breakfast.

8:30

General Medical Clinics: Exhibition of Patients showing Conditions Reviewed during Course.

Drs. Watson and Associates.

12:30

Luncheon.

Certificates of Attendance.

## COURSE NO. 4—ALLERGY

(October 16-21, 1944)

ROOSEVELT HOSPITAL

New York, N. Y.

ROBERT A. COOKE, M.D., F.A.C.P., *Director*

(Minimal Registration, 25; Maximal Registration, 50)

## OFFICERS OF INSTRUCTION

Robert A. Cooke, M.D., F.A.C.P., Attending Physician and Director, Department of Allergy, Roosevelt Hospital.

Horace S. Baldwin, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Assistant Attending Physician and Chief of Allergy Clinic, New York Hospital.

Aaron Brown, M.D., Assistant Clinical Professor of Medicine and Chief of Allergy Clinic, New York University College of Medicine; Assistant Visiting Physician, Bellevue Hospital.

Robert Chobot, M.D., F.A.C.P., Assistant Professor of Clinical Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Pediatric Allergy, New York Post-Graduate Medical School and Hospital; Assistant Chief, Allergy Clinic, Roosevelt Hospital.

Russell Clark Grove, M.D., Associate Surgeon, Otolaryngology, Roosevelt Hospital.

Joseph Harkavy, M.D., Associate in Medicine, Columbia University College of Physicians and Surgeons; Associate Physician and Chief of Allergy Clinic, Mt. Sinai Hospital; Associate Physician, Montefiore Hospital.

Seliam Hebard, M.D., Assistant Chief of Allergy Clinic, Roosevelt Hospital; Senior Clinical Assistant in Allergy, Outpatient Department, Mt. Sinai Hospital.

Paul Klemperer, M.D., Pathologist, Mt. Sinai Hospital.

Louis Schwartz, M.D., Medical Director, Chief, Dermatoses Section, U. S. Public Health Service, Bureau of State Services, Bethesda, Md.

Will Cook Spain, M.D., F.A.C.P., Clinical Professor of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Allergy Clinic and Attending Physician, New York Post-Graduate Medical School and Hospital.

Albert Vander Veer, M.D., Consultant in Allergy and Chief of Allergy Clinic, Roosevelt Hospital.

Matthew Walzer, M.D., Associate in Medicine, Cornell University Medical College; Attending in Allergy and Chief of Allergy Clinic, Jewish Hospital, Brooklyn.

The course in Allergy this year will be given in its entirety at the Roosevelt Hospital, but the faculty will be drawn from various medical schools and hospitals in New York and from the U. S. Public Health Service.

Instruction will be by means of lectures, clinics and conferences. All phases of allergy—immunological, pathological and clinical—will be considered from their practical and theoretical aspects. The course is planned to furnish the internist, general practitioner or allergist with the soundest and most recent information on concepts and procedures for diagnosis and treatment, and the general management of the allergic patient. On Saturday morning (October 21), there will be an optional morning session for those interested in preparation of allergenic extracts or desirous of practical experience in the technique of skin testing. A reference list of desirable articles on allergy will be mailed to all registrants from the office of the American College of Physicians.

Invitation to register for this particular course is extended beyond members of the American College of Physicians to members of the American Academy of Allergy, and to any members of the Inter-American Group who are pursuing postgraduate study in this Country at this time.

## OUTLINE OF COURSE

Monday, October 16.

## A.M. Session

9:00-11:30 Registration.

Introduction to Allergy.

Dr. Cooke.

11:30- 1:00 Extracts: Methods of Preparation and Standardization.

Dr. Spain.

## P.M. Session

2:00- 4:00 Techniques of Skin Testing and Their Interpretation.

Dr. Walzer.

4:00- 6:00 Histopathology of the Allergic Reaction.

Dr. Klemperer.

7:30 Informal Dinner.

Tuesday, October 17.

## A.M. Session

9:00-11:30 Pediatric Allergy (1st session).

Dr. Chobot.

11:30- 1:00 Allergic Coryza-Perennial.

Dr. Vander Veer.

## P.M. Session

2:00- 4:00 Non-Infective Asthma.

Dr. Spain.

4:00- 6:00 Allergic Coryza-Seasonal (1st session).

Dr. Vander Veer.

Wednesday, October 18.

## A.M. Session

9:00-10:30 Allergic Coryza-Seasonal (2nd session).

Dr. Brown.

10:30-11:30 Allergic Coryza-Seasonal, Special Features.

Dr. Hebal.

11:30- 1:00 Vascular Allergy; Meniere's Disease; Migraine; Physical Allergy.

Dr. Harkavy.

## P.M. Session

2:00- 4:00 Industrial Dermatoses.

Dr. Schwartz.

4:00- 6:00 Sinus Disease in Relation to Allergy.

Dr. Grove.

Thursday, October 19.

## A.M. Session

9:00-10:30 Serum Disease; Drug and Insulin Allergy.

Dr. Harkavy.

10:30-12:30 Asthma: Differential Diagnosis; Symptomatic Treatment of Status Asthmaticus.

Dr. Baldwin.

P.M. Session

2:00- 3:30 Pediatric Allergy (2nd session).

Dr. Chobot.

3:30- 6:00 Infective Asthma.

Dr. Cooke.

Friday, October 20.

A.M. Session

9:00-12:30 Eczema, Urticaria, Angioneurotic Edema and Miscellaneous Allergies, with Case Presentations.

Dr. Cooke.

P.M. Session

2:00- 5:00 General Review and Roundtable.

By coincidence, the American College of Physicians will be conducting a Regional Meeting for the State of New York in New York City, Friday, October 20. Announcements concerning the program will be furnished to all registrants in this course. However, all are invited to attend the regional dinner meeting from 6:00 to 8:00 P.M. at the Waldorf-Astoria Hotel, and to be the guests of the New York Academy of Medicine at 8:30 P.M. at a Panel Discussion on "The Evaluation of Sulfa Drugs and Penicillin," a feature of the Seventeenth Graduate Fortnight at the Academy. Dr. David P. Barr, F.A.C.P., will be the Chairman of the Panel Discussion, and Drs. Rene J. Dubos, Colin M. MacLeod, John F. Mahoney, Frank L. Meleney and William S. Tillett will assist.

Saturday, October 21.

A.M. Session

9:00 Optional. Practical Work, Tests, Extracts and Clinic Management.  
Drs. Cooke and Spain.

## COURSE NO. 5—SPECIAL PHASES OF INTERNAL MEDICINE

(October 23-November 4, 1944)

CHICAGO INSTITUTIONS

THORNE HALL

NORTHWESTERN UNIVERSITY

Lake Shore Drive and Superior Street

Chicago, Ill.

WILLARD O. THOMPSON, M.D., F.A.C.P., *Director*

WALTER L. PALMER, M.D., F.A.C.P., *Governor for Northern Illinois*

(Minimal Registration, 25; Maximal Registration, 60)

This course offers an unusual opportunity for physicians to familiarize themselves with recent developments in various fields of Internal Medicine. The faculty of 110 men includes many of the most outstanding physicians, not only in Chicago, but also from other parts of the country. Numerous Chicago Institutions are represented, including the University of Chicago, University of Illinois, Northwestern University,

Loyola University, the Institute of Psychoanalysis, the Illinois Neuropsychiatric Institute, the Michael Reese Hospital, as are also many outside agencies and institutions, including Harvard Medical School, Ohio State University, University of Michigan, University of Minnesota, Washington University, University of Oklahoma, University of Cincinnati, State University of Iowa, Marquette University, the Cleveland Clinic, Indianapolis City Hospital, the Medical Corps of the U. S. Army and the U. S. Navy, and the U. S. Public Health Service. Where possible, clinical discussions will be illustrated by demonstration of patients.

*Meeting Place:* Thorne Hall, Northwestern University, Lake Shore Drive and Superior Street—All sessions will be held in Thorne Hall, except those on Saturday, November 4, which will be held in the Drake Hotel. This day will be devoted to the Regional Meeting of the American College of Physicians for the States of Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin. This meeting is part of the course, and all physicians taking the course, whether they be members of the College or not, are invited not only to participate in the scientific sessions of the Regional Meeting, but also to attend the luncheon and the dinner.

*Luncheon:* Abbott Hall, Northwestern University, 710 Lake Shore Drive—Abbott Hall is just across the street from Thorne Hall.

#### OFFICERS OF INSTRUCTION

William E. Adams, M.D., F.A.C.S., Associate Professor of Surgery, University of Chicago, The School of Medicine.

Wright R. Adams, M.D., Associate Professor of Medicine, University of Chicago, The School of Medicine.

Edgar V. Allen, F.A.C.P., Col., (MC), AUS, Consultant in Medicine, Seventh Service Command, Omaha, Nebr.

Raymond B. Allen, M.D., Dean, University of Illinois College of Medicine.

Howard Alt, M.D., Assistant Professor of Medicine, Northwestern University Medical School.

Edwin B. Astwood, M.D., Assistant Professor of Pharmacotherapy, Harvard Medical School, Boston, Mass.

Percival Bailey, M.D., Professor of Neurology and Neurosurgery, University of Illinois College of Medicine.

Clifford Barborka, M.D., F.A.C.P., Assistant Professor of Medicine and Director, Abbott Foundation for Medical Research, Northwestern University Medical School.

Claude S. Beck, F.A.C.S., Lt. Col., (MC), AUS, Consultant in Surgery, Fifth Service Command, Columbus, Ohio.

Granville Bennett, M.D., Professor of Pathology, University of Illinois College of Medicine.

Robert S. Berghoff, M.D., F.A.C.P., Clinical Professor of Medicine, Loyola University School of Medicine; President-Elect, Illinois State Medical Society.

Bert I. Beverly, M.D., Assistant Professor of Pediatric Psychiatry, University of Illinois College of Medicine.

Marion A. Blankenhorn, M.D., F.A.C.P., Professor of Medicine and Head of the Department, University of Cincinnati College of Medicine, Cincinnati, Ohio.

William J. Bleckwenn, Col., (MC), AUS, Consultant in Neuropsychiatry, Sixth Service Command, Chicago. (Formerly, Surgeon in the forward echelon, Southwest Pacific Area.)

Robert G. Bloch, M.D., F.A.C.P., Professor of Medicine and Chief of the Division of Pulmonary Diseases, University of Chicago, The School of Medicine.

Alexander Brunschwig, M.D., F.A.C.S., Professor of Surgery, University of Chicago, The School of Medicine.



- Paul R. Cannon, M.D., Professor and Chairman of the Department of Pathology, University of Chicago, The School of Medicine.
- Charles M. Caravati, F.A.C.P., Lt. Col., (MC), AUS, Physician-in-Chief, Percy Jones General Hospital, Battle Creek, Mich.
- Anton J. Carlson, M.D., F.A.C.P., Professor of Physiology, Emeritus, University of Chicago, The School of Medicine.
- Warren H. Cole, M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Illinois College of Medicine.
- Arthur R. Colwell, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School.
- Edward L. Compere, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School; Chairman, Department of Orthopedic Surgery, Wesley Memorial Hospital.
- Robert M. Craig, M.D., Passed Assistant Surgeon (R), U. S. Public Health Service, Chicago.
- Irving S. Cutter, M.D., Professor of Medicine, Emeritus, Northwestern University Medical School.
- Israel Davidsohn, M.D., F.A.C.P., Assistant Professor of Pathology, University of Illinois College of Medicine; Pathologist and Director of Laboratories, Mt. Sinai Hospital.
- Geza de Takats, M.D., F.A.C.S., Associate Professor of Surgery, University of Illinois College of Medicine.
- Charles A. Doan, M.D., F.A.C.P., Professor of Medicine and Chairman of the Department, Ohio State University College of Medicine, Columbus, Ohio.
- Lester R. Dragstedt, M.D., F.A.C.P., Professor of Surgery, University of Chicago, The School of Medicine.
- Samuel M. Feinberg, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School.
- Morris Fishbein, M.D., Assistant Professor of Medicine, University of Illinois College of Medicine; Editor, Journal of the American Medical Association.
- Thomas M. Francis, M.D., Professor of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Mich.
- Thomas M. French, M.D., Assistant Director, Institute of Psychoanalysis.
- Lee C. Gatewood, M.D., F.A.C.P., Professor of Medicine (Rush), University of Illinois College of Medicine.
- Francis J. Gerty, M.D., Professor of Psychiatry and Head of the Department, University of Illinois College of Medicine; Director, Psychiatric Division, Illinois Neuropsychiatric Institute.
- Stanley Gibson, M.D., Professor of Pediatrics and Head of the Department, Northwestern University Medical School.
- Newell C. Gilbert, M.D., Professor of Medicine and Head of the Department, Northwestern University Medical School.
- Carl G. Hartman, Ph.D., Professor and Head of the Department of Zoology and Physiology, University of Illinois, Urbana, Ill.
- B. C. H. Harvey, M.D., Dean of Medical Students, The University of Chicago.
- Jerome R. Head, M.D., Assistant Professor of Surgery, Northwestern University Medical School; Medical Director, Edward Sanitarium, Naperville, Ill.
- Norris J. Heckel, M.D., F.A.C.S., Associate Professor of Urology (Rush), University of Illinois College of Medicine.
- Don G. Hildrup, Colonel, (MC), USA, Surgeon, Sixth Service Command, Chicago, Ill.
- Paul H. Holinger, M.D., F.A.C.S., Assistant Professor of Otolaryngology, University of Illinois College of Medicine.

- Archibald L. Hoyne, M.D., F.A.C.P., Professor of Pediatrics, University of Illinois College of Medicine; Clinical Professor of Pediatrics, University of Chicago, The School of Medicine.
- Charles B. Huggins, M.D., Professor of Surgery (Genito-urinary), University of Chicago, The School of Medicine.
- Ernest E. Irons, M.D., F.A.C.P., Professor of Medicine, University of Illinois College of Medicine; President, American College of Physicians.
- Raphael Isaacs, M.D., F.A.C.P., Attending Physician in Hematology and Director, Laboratory of Hematology, Michael Reese Hospital.
- Andrew C. Ivy, M.D., F.A.C.P., Nathan Smith Davis Professor of Physiology, Northwestern University Medical School.
- Louis N. Katz, M.D., F.A.C.P., Professorial Lecturer in Physiology, University of Chicago, The School of Medicine; Head of the Division of Cardiovascular Research, Michael Reese Hospital.
- Robert Wood Keeton, M.D., F.A.C.P., Professor of Medicine and Head of the Department, University of Illinois College of Medicine.
- Norman M. Keith, M.D., Professor of Medicine, Mayo Foundation, University of Minnesota; Consulting Physician, Mayo Clinic; Rochester, Minn.
- Frank B. Kelly, M.D., F.A.C.P., Professor of Medicine (Rush), University of Illinois College of Medicine.
- Edward C. Kendall, M.D., Professor of Biochemistry, Mayo Foundation, University of Minnesota, Rochester, Minn.
- Allen T. Kenyon, M.D., Associate Professor of Medicine, University of Chicago, The School of Medicine.
- Fred C. Koch, Ph.D., Professor of Biochemistry, Emeritus, University of Chicago.
- Peter C. Kronfeld, M.D., Associate Professor of Ophthalmology and Director of Education, Illinois Eye & Ear Infirmary, University of Illinois College of Medicine.
- Grant H. Laing, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School.
- Sidney O. Levinson, M.D., Director, Samuel Deutsch Serum Center, Michael Reese Hospital.
- Louis R. Limarzi, M.D., Assistant Professor of Medicine, University of Illinois College of Medicine.
- John R. Lindsay, M.D., Professor of Otolaryngology, University of Chicago, The School of Medicine.
- Malcolm T. MacEachern, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School; Director of Program of Hospital Administration, Northwestern University School of Commerce; Chairman of the Administrative Board, American College of Surgeons.
- Paul B. Magnuson, M.D., F.A.C.S., Professor of Bone and Joint Surgery and Head of the Department, Northwestern University Medical School.
- Chauncey C. Maher, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School.
- David E. Markson, M.D., F.A.C.P., Associate Professor of Medicine and Director of the Arthritis Clinic, Northwestern University Medical School.
- Donald McCarthy, F.A.C.P., Captain, (MC), USN, Professional Executive Officer, U. S. Naval Hospital, Great Lakes, Ill.
- E. P. McCullagh, M.D., F.A.C.P., Head of Endocrine Research Laboratory, Cleveland Clinic Foundation Hospital, Cleveland, Ohio.
- Warren S. McCulloch, M.D., Associate Professor of Psychiatry, University of Illinois College of Medicine.
- Ross T. McIntire, F.A.C.P., Vice Admiral, (MC), USN, Surgeon General, U. S. Navy, Washington, D. C.

- Phillip Miller, M.D., Professor of Medicine, University of Chicago, The School of Medicine.
- James H. Mitchell, M.D., Professor of Dermatology (Rush), University of Illinois College of Medicine.
- Herman J. Moersch, M.D., F.A.C.P., Associate Professor of Medicine, Mayo Foundation, University of Minnesota, Rochester, Minn.
- Carl R. Moore, Ph.D., Professor and Head of the Department of Zoology, University of Chicago.
- Carl V. Moore, Jr., M.D., F.A.C.P., Associate Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.
- Josiah J. Moore, M.D., F.A.C.P., Director, Moore Clinical Laboratory; President, Chicago Medical Society.
- Walter H. Nadler, M.D., Associate Professor of Medicine, Northwestern University Medical School.
- Warren O. Nelson, M.D., Professor of Anatomy, State University of Iowa College of Medicine, Iowa City, Iowa.
- Eric Oldberg, M.D., F.A.C.S., Professor of Neurology and Neurological Surgery and Head of the Department, University of Illinois College of Medicine.
- Irvine H. Page, M.D., F.A.C.P., Director, Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Ind.
- Walter L. Palmer, M.D., F.A.C.P., Professor of Medicine, University of Chicago, The School of Medicine.
- Max M. Peet, M.D., F.A.C.S., Professor of Surgery, University of Michigan Medical School, Ann Arbor, Mich.
- Carl M. Peterson, M.D., Secretary, Council on Industrial Health, American Medical Association.
- Dallas B. Phemister, M.D., F.A.C.S., Thomas D. Jones Professor of Surgery and Head of the Department, University of Chicago, The School of Medicine.
- Sidney A. Portis, M.D., F.A.C.P., Associate Professor of Medicine (Rush), University of Illinois College of Medicine.
- Frank B. Queen, F.A.C.P., Lt. Col., (MC), AUS; Chief of Laboratory Service, Bushnell General Hospital, Brigham City, Utah.
- Armand J. Quick, Ph.D., M.D., Professor of Biochemistry and Head of the Department, Marquette University School of Medicine, Milwaukee, Wis.
- Paul S. Rhoads, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School.
- Henry T. Ricketts, M.D., Associate Professor of Medicine, University of Chicago, The School of Medicine.
- Stephen Rothman, M.D., Associate Professor of Medicine and Head of the Section of Dermatology and Syphilology, University of Chicago, The School of Medicine.
- George J. Rukstinat, M.D., Professor of Pathology, University of Illinois College of Medicine.
- Edward H. Ryneerson, M.D., F.A.C.P., Associate Professor of Medicine, Mayo Foundation, University of Minnesota, Rochester, Minn.
- George X. Schwemlein, M.D., Passed Assistant Surgeon (R), U. S. Public Health Service, Chicago.
- George W. Scupham, M.D., Associate Professor of Medicine, Northwestern University Medical School.
- Francis E. Seneat, M.D., F.A.C.P., Professor of Dermatology and Head of the Department, University of Illinois College of Medicine.
- James P. Simonds, M.D., Professor of Pathology, Emeritus, Northwestern University Medical School.
- David Slight, M.D., Professor of Psychiatry, University of Chicago, The School of Medicine.

- LeRoy H. Sloan, M.D., F.A.C.P., Professor of Medicine, University of Illinois College of Medicine.
- Lowell D. Snorf, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School.
- Samuel Soskin, M.D., Professorial Lecturer in Physiology, University of Chicago, The School of Medicine; Medical Director, Michael Reese Hospital.
- Ralph Soto-Hall, Major, (MC), AUS, Consultant in Orthopedic Surgery, Sixth Service Command, Chicago. (Formerly, Consultant in the European Theater of Operations.)
- Wesley W. Spink, M.D., F.A.C.P., Associate Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minn.
- Henry C. Sweany, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School; Professorial Lecturer in the Department of Pharmacology, University of Chicago; Medical Director of Research and Laboratories, Municipal Tuberculosis Sanitarium.
- Frederic E. Templeton, M.D., Cleveland Clinic, Cleveland, Ohio.
- Willard O. Thompson, M.D., F.A.C.P., Professor of Medicine (Rush), University of Illinois College of Medicine.
- Henry H. Turner, M.D., F.A.C.P., Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.
- Theodore R. Van Dellen, M.D., F.A.C.P., Associate Professor of Medicine and Head of the Cardiac Clinic, Northwestern University Medical School.
- Adrien H. P. E. Verbrugghen, M.D., F.A.C.S., Associate Professor of Neurological Surgery (Rush), University of Illinois College of Medicine.
- Italo F. Volini, M.D., F.A.C.P., Professor and Head of the Department of Medicine and Dean of the School of Medicine, Loyola University.
- George E. Wakerlin, M.D., F.A.C.P., Professor of Physiology and Head of the Department, University of Illinois College of Medicine.
- Cecil J. Watson, M.D., F.A.C.P., Professor of Medicine and Head of the Department, University of Minnesota Medical School, Minneapolis, Minn.
- Irving S. Wright, F.A.C.P., Lt. Col., (MC), AUS, Consultant in Medicine, Sixth Service Command, Chicago.
- Frederick A. Willius, M.D., F.A.C.P., Head of the Section on Cardiology, Mayo Clinic; Associate Professor of Medicine, Mayo Foundation, University of Minnesota; Rochester, Minn.

#### OUTLINE OF COURSE

Monday, October 23.

#### *Cardiovascular and Renal Diseases*

WILLARD O. THOMPSON, M.D., F.A.C.P., *Presiding*

#### A.M. Session

7:30- 8:30 Registration.

Thorne Hall, Lake Shore Drive and Superior Street.

8:30- 9:00 Diagnosis of Congenital Heart Disease.

Dr. W. R. Adams.

9:00- 9:30 Rheumatic Fever in Children.

Dr. Gibson.

9:30-10:00 Rheumatic Fever: Correlation of Clinical and Pathologic Findings.

Dr. Simonds.

10:00-10:30 Rheumatic Heart Disease. The Sequence of Pathologic Changes as They Affect the Heart.

Dr. Volini.

- 10:30-10:45 Intermission—Refreshments.  
 10:45-11:15 Rheumatic Fever in the Army.  
                   Lt. Col. Wright.  
 11:15-11:45 Rheumatic Fever in the Navy.  
                   Capt. McCarthy.  
 11:45-12:15 Rheumatic Carditis.  
                   Dr. Willius.  
 12:15-12:45 Management of Cardiac Edema.  
                   Dr. Maher.  
 12:45- 1:15 Pathogenesis of Subacute Bacterial Endocarditis.  
                   Dr. Willius.  
 1:15- 2:15 Luncheon.

Monday October 23.

*Cardiovascular and Renal Diseases (Continued)*

ITALO F. VOLINI, M.D., F.A.C.P., *Presiding*

P.M. Session

- 2:15- 2:45 The Factors Influencing Recovery or Death in Acute Coronary  
                   Occlusion.  
                   Dr. Willius.  
 2:45- 3:15 Clinical Aspects of the Control of Coronary Circulation.  
                   Dr. Katz.  
 3:15- 3:45 The Surgical Approach to Coronary Disease.  
                   Lt. Col. Beck.  
 3:45- 4:15 Constrictive Pericarditis.  
                   Dr. Willius.  
 4:15- 4:30 Intermission—Refreshments.  
 4:30- 5:00 Compression of the Heart.  
                   Lt. Col. Beck.  
 5:00- 5:30 Less Familiar Vascular Syndromes.  
                   Dr. Sloan.  
 5:30- 5:50 Discussion.

Tuesday, October 24.

*Cardiovascular and Renal Diseases (Continued)*

MORRIS FISHBEIN, M.D., *Presiding*

A.M. Session

- 8:00- 8:30 Recent Advances in the Utility of the Electrocardiogram in Clinical  
                   Practice.  
                   Dr. Katz.  
 8:30- 9:00 Surgical Treatment of Hypertension.  
                   Dr. Peet.  
 9:00- 9:30 Essential Hypertension: Clinical Groups and Their Course.  
                   Dr. Keith.  
 9:30-10:00 Hypertension and Bright's Disease.  
                   Dr. Page.  
 10:00-10:30 Hypertension Heart Disease.  
                   Dr. Nadler.  
 10:30-10:45 Intermission—Refreshments.  
 10:45-11:15 Arteriosclerosis.  
                   Dr. Van Dellen.

- 11:15-11:45 Acute Nephritis Including Acute Renal Insufficiency; Course and Prognosis.  
Dr. Keith.
- 11:45-12:15 Diagnosis and Treatment of Common Urinary Infections.  
Dr. Heckel.
- 12:15-12:45 Chronic Glomerulonephritis; Course and Prognosis.  
Dr. Keith.
- 12:45- 1:15 Ophthalmoscopy in the Diagnosis of Human Illness.  
Dr. Kronfeld.
- 1:15- 2:15 Luncheon.

Tuesday, October 24.

*Cardiovascular and Renal Diseases (Continued)*

DON G. HILDRUP, Colonel, (MC), USA, *Presiding*

P.M. Session

- 2:15- 2:45 Newer Concepts Regarding Uremia.  
Dr. Keith.
- 2:45- 3:25 Peripheral Vascular Disease.  
Lt. Col. Wright.
- 3:25- 3:55 Surgical Treatment of Peripheral Vascular Disease.  
Dr. de Takats.
- 3:55- 4:15 Sympathectomy in the Treatment of Peripheral Vascular Disease.  
Dr. Peet.
- 4:15- 4:30 Intermission—Refreshments.
- 4:30- 5:00 Periarteritis Nodosa.  
Dr. Scupham.
- 5:00- 5:30 Shock.  
Dr. Page.
- 5:30- 5:50 Discussion.

Wednesday, October 25.

*Arthritis*

JOSIAH J. MOORE, M.D., F.A.C.P., *Presiding*

A.M. Session

- 8:00- 8:30 Surgical Phases of Arthritis.  
Dr. Compere.
- 8:30- 9:00 Classification and Treatment of Arthritis.  
Dr. Markson.
- 9:00- 9:30 Comparison of Different Forms of Arthritis.  
Dr. Bennett.
- 9:30-10:00 The Differential Diagnosis of Conditions that Cause Low Back Pain Accompanied by Sciatica.  
Dr. Magnuson.

*Industrial Medicine*

- 10:00-10:30 Industry Needs the Physician.  
Dr. Peterson.
- 10:30-10:45 Intermission—Refreshments.

*Pulmonary Diseases*

- 10:45-11:15 Tuberculosis Control in General Medical Practice.  
Dr. Bloch.

- 11:15-11:45 Surgical Treatment of Pulmonary Tuberculosis.  
Dr. Head.
- 11:45-12:15 Diagnosis of Non-Tuberculous Pulmonary Lesions with Special Reference to Silicosis.  
Dr. Sweany.
- 12:15-12:45 Aspiration Pneumonia.  
Dr. Irons.
- 12:45- 1:15 The Confusing Clinical Picture of Atypical Primary Bronchial Pneumonia.  
Dr. Rhoads.
- 1:15- 2:15 Luncheon.

Wednesday, October 25.

*Pulmonary Diseases (Continued)*

LEROY H. SLOAN, M.D., F.A.C.P., *Presiding*

P.M. Session

- 2:15- 2:45 Differential Diagnosis and Treatment of Intrathoracic Tumors.  
Dr. W. E. Adams.
- 2:45- 3:30 Bronchial Tumors.  
Dr. Holinger.

*Neurology and Psychiatry*

- 3:30- 4:00 Pathology and Symptomatology of the Hypothalamus.  
Dr. Bailey.
- 4:00- 4:15 Intermission—Refreshments.
- 4:15- 4:45 Intervertebral Discs.  
Dr. Oldberg.
- 4:45- 5:15 Meniere's Syndrome.  
Dr. Lindsay.
- 5:15- 5:45 Relation of Psychoanalysis to Internal Medicine.  
Dr. French.

Thursday, October 26.

*Neurology and Psychiatry (Continued)*

WALTER L. PALMER, M.D., F.A.C.P., *Presiding*

A.M. Session

- 8:00- 8:30 Some Physiological Aspects of Mental Disorder.  
Dr. McCulloch.
- 8:30- 9:00 Psychological Problems in the General Hospital.  
Dr. Gerty.
- 9:00- 9:30 Psychological Problems of the Adolescent.  
Dr. Beverly.
- 9:30-10:00 Psychotherapy in General Medicine.  
Dr. Slight.

*Gastrointestinal Diseases*

ERNEST E. IRONS, M.D., F.A.C.P., *Presiding*

- 10:00-10:30 Management of Peptic Ulcer.  
Dr. Palmer.
- 10:30-10:45 Intermission—Refreshments.

- 10:45-11:30 Management of Peptic Ulcer (Continued).  
Dr. Palmer.
- 11:30-12:00 The Technics of Roentgenologic Examination of the Oesophagus, Stomach and Duodenum.  
Dr. Templeton.
- 12:00-12:45 Recent Contributions to the Physiology of the Gastrointestinal Tract.  
Dr. Ivy.
- 12:45- 1:15 The Normal Oesophagus, Stomach and Duodenum.  
Dr. Templeton.
- 1:15- 2:15 Luncheon.

Thursday, October 26.

*Gastrointestinal Diseases (Continued)*

WALTER L. PALMER, M.D., F.A.C.P., *Presiding*

P.M. Session

- 2:15- 2:45 Diagnosis and Treatment of Oesophageal Disease.  
Dr. Moersch.
- 2:45- 3:15 Surgical Treatment of Lesions of Lower Oesophagus.  
Dr. Phemister.
- 3:15- 3:45 Abnormalities of the Oesophagus, Stomach and Duodenum.  
Dr. Templeton.
- 3:45- 4:15 Differential Diagnosis of Cardiospasm.  
Dr. Moersch.
- 4:15- 4:30 Intermission—Refreshments.
- 4:30- 5:00 Inflammatory Conditions of the Oesophagus, Stomach and Duodenum.  
Dr. Templeton.
- 5:00- 5:45 Clinico-Pathologic Conference.  
Drs. Sloan and Simonds.

Friday, October 27.

*Gastrointestinal Diseases (Continued)*

GRANT H. LAING, M.D., F.A.C.P., *Presiding*

A.M. Session

- 8:00- 8:30 Relation between Deficiency Diseases and the Gastrointestinal Tract.  
Dr. Barborka.
- 8:30- 9:30 Natural History of Carcinoma of the Stomach.  
Dr. Palmer.
- 9:30-10:00 The Value of Gastroscoy in the Study of Gastric Distress following Gastric Surgery.  
Dr. Moersch.
- 10:00-10:30 Dyspepsia.  
Dr. Palmer.
- 10:30-10:45 Intermission—Refreshments.

WALTER L. PALMER, M.D., F.A.C.P., *Presiding*

- 10:45-11:15 Surgical Treatment of Peptic Ulcer.  
Dr. Cole.
- 11:15-11:45 Section of the Vagus Nerve in the Treatment of Gastro-duodenal Ulcer.  
Dr. Dragstedt.
- 11:45-12:15 Isolated Ulcerative Lesions of the Intestine.  
Lt. Col. Caravati.



12:15-12:45 Non-specific Ulcerative Colitis.

Dr. Snorf.

12:45- 1:15 The Extension of Surgical Attack upon Advanced Intro-abdominal Cancer.

Dr. Brunschwig.

1:15- 2:15 Luncheon.

Friday, October 27.

*Gastrointestinal Diseases (Continued)*

WALTER L. PALMER, M.D., F.A.C.P., *Presiding*

P.M. Session

2:15- 2:45 Amebiasis.

Dr. Gatewood.

2:45- 3:15 Psychosomatic Aspects of the Gastrointestinal Tract.

Dr. Portis.

3:15- 3:45 Surgical Treatment of Ulcerative Colitis.

Dr. Dragstedt.

3:45- 4:15 Diseases of the Gall Bladder.

Dr. Cole.

4:15- 4:30 Intermission—Refreshments.

4:30- 5:15 Applied Physiology of the Gall Bladder.

Dr. Ivy.

5:15- 5:45 Hepatitis.

Lt. Col. Caravati.

Saturday, October 28.

*Gastrointestinal Diseases (Continued)*

PAUL S. RHOADS, M.D., F.A.C.P., *Presiding*

A.M. Session

8:00- 8:30 Cirrhosis of the Liver.

Dr. Nadler.

8:30- 9:15 Liver Function Tests.

Dr. Ivy.

9:15-10:00 The Protein Problem.

Dr. Cannon.

*Dermatology*

10:00-10:30 Dermatitis Medicamentosa.

Dr. Senear.

10:30-10:45 Intermission—Refreshments.

10:45-11:15 Cutaneous Diseases in Relation to Internal Disturbances.

Dr. Rothman.

11:15-11:45 Fungus Infections of the Skin.

Dr. Mitchell.

11:45-12:15 Modern Conceptions of Eczema.

Dr. Senear.

12:15-12:45 Rôle of Allergy in Dermatology.

Dr. Feinberg.

12:45- 1:15 Recent Advances in the Treatment of Syphilis.

Drs. Craig and Schwemlein.

1:15- 2:15 Luncheon.

Monday, October 30.

*Endocrinology*

WILLARD O. THOMPSON, M.D., F.A.C.P., *Presiding*

A.M. Session

- 8:00- 8:30 Selection of Insulin in Diabetic Therapy.  
Dr. Colwell.
- 8:30- 9:00 Treatment of Diabetic Acidosis.  
Dr. Ricketts.
- 9:00- 9:30 The Surgery of Malignant Pancreatic Tumors.  
Dr. Brunschwig.
- 9:30-10:30 Practical Considerations in the Management of Diabetic Patients  
(Clinic).  
Dr. Keeton.
- 10:30-10:45 Intermission—Refreshments.
- 10:45-11:45 Practical Considerations in the Management of Diabetic Patients  
(Clinic Continued).  
Dr. Keeton.
- 11:45-12:15 Types of Diabetes Mellitus and their Treatment.  
Dr. Colwell.
- 12:15-12:45 Hyperinsulinism.  
Dr. Ryneerson.
- 12:45- 1:15 Production of Pseudohermaphroditism.  
Dr. Ivy.
- 1:15- 2:15 Luncheon.

Monday, October 30.

*Endocrinology (Continued)*

MALCOLM T. MACEachern, M.D., F.A.C.P., *Presiding*

P.M. Session

- 2:15- 3:15 The Normal and Hyperactive Ovary in Relation to the Menstrual Cycle.  
Dr. Hartman.
- 3:15- 3:45 Carcinoma of the Prostate.  
Dr. Huggins.
- 3:45- 4:15 Evaluation of Sex Hormones in the Treatment of Some Urologic  
Diseases.  
Dr. Heckel.
- 4:15-4:30 Intermission—Refreshments.
- 4:30- 5:30 Diseases of the Pituitary.  
Dr. Ryneerson.
- 5:30- 5:50 Discussion.

Tuesday, October 31.

*Endocrinology (Continued)*

IRVING S. CUTTER, M.D., *Presiding*

A.M. Session

- 8:00- 8:30 Factors in Puberty.  
Dr. Kenyon.
- 8:30- 9:00 Endocrine Factors in Human Puberty.  
Dr. Nelson.

- 9:00-10:00 The Interpretation of Data on the Male Sex Hormone; 17-Keto-Steroid Content of Human Urine.  
Dr. Koch.
- 10:00-10:30 Addison's Disease, Emphasizing Diagnostic Tests and Limitations of Desoxycorticosterone Therapy.  
Dr. McCullagh.
- 10:30-10:45 Intermission—Refreshments.
- 10:45-11:15 Surgical Diagnosis of Pituitary Tumor.  
Dr. Verbrugghen.
- 11:15-11:45 Some Clinical Aspects of Dwarfism.  
Dr. McCullagh.
- 11:45-12:30 Endocrine Clinic: Hypogonadism.  
Dr. Thompson.
- 12:30- 1:15 Endocrine Organs in Early Life and Some Associated Disorders.  
Dr. C. R. Moore.
- 1:15- 2:15 Luncheon.

Tuesday, October 31.

*Endocrinology (Continued)*

RAYMOND B. ALLEN, M.D., *Presiding*

P.M. Session

- 2:15- 3:15 Endocrine Clinic: Hypogonadism (Continued).  
Dr. Thompson.
- 3:15- 3:45 Disorders of Reproduction in the Human Male.  
Dr. Nelson.
- 3:45- 4:15 Types of Testicular Failure and Their Management.  
Dr. McCullagh.
- 4:15- 4:30 Intermission—Refreshments.
- 4:30- 5:00 Results of Seven Years of Clinical Experience with Testosterone Propionate.  
Dr. Turner.
- 5:00- 5:30 Hormonal Therapy in Menstrual Disorders.  
Dr. McCullagh.
- 5:30- 5:50 Discussion.

Wednesday, November 1.

*Endocrinology (Continued)*

GEORGE E. WAKERLIN, M.D., F.A.C.P., *Presiding*

A.M. Session

- 8:00- 9:00 Endocrine Clinic: Hypogonadism (Continued).  
Dr. Thompson.
- 9:00- 9:30 Endocrine Physiology of the Breast.  
Dr. Nelson.
- 9:30-10:00 Endocrine Dwarfism; Its Diagnosis and Treatment.  
Dr. Turner.
- 10:00-10:30 Treatment of Dwarfism.  
Dr. Thompson.
- 10:30-10:45 Intermission—Refreshments.
- 10:45-11:15 Treatment of Dwarfism (Continued).  
Dr. Thompson.
- 11:15-11:45 Influence of the Adrenals on Carbohydrate Metabolism.  
Dr. Kendall.

- 11:45-12:15 Experimental Production of Mammary Carcinoma.  
Dr. Nelson.
- 12:15-12:45 Persistence of Estrogenic Effects after Discontinuance of Treatment.  
Dr. Turner.
- 12:45- 1:15 Obesity.  
Dr. Soskin.
- 1:15- 2:15 Luncheon.

Wednesday, November 1.

*Endocrinology (Continued)*

ROBERT W. KEETON, M.D., F.A.C.P., *Presiding*

P.M. Session

- 2:15- 2:45 Chemistry of Anti-thyroid Compounds, with Special Reference to  
Thiouracil and Hyperthyroidism.  
Dr. Astwood.
- 2:45-3:45 Endocrine Clinic: Treatment of Toxic Goiter.  
Dr. Thompson.
- 3:45- 4:15 Diagnosis and Treatment of Obesity.  
Dr. Turner.
- 4:15- 4:30 Intermission—Refreshments.
- 4:30- 5:00 Influence of the Adrenals on Tumors of Lymphatic Origin in the  
Mouse.  
Dr. Kendall.
- 5:00- 5:45 Clinico-Pathologic Conference.  
Drs. Sloan and Rukstinat.

Thursday, November 2.

*Endocrinology (Continued)*

ANTON J. CARLSON, M.D., F.A.C.P., *Presiding*

A.M. Session

- 8:00- 9:00 Endocrine Clinic: Addison's Disease.  
Dr. Thompson.
- 9:00- 9:30 Control of Corpus Luteum Function.  
Dr. Astwood.
- 9:30-10:00 The Treatment of Coronary Thrombosis.  
Dr. Gilbert.

*Infectious Diseases*

- 10:00-10:30 Declining Trends and Future Management of Acute Infectious  
Diseases.  
Dr. Hoyne.
- 10:30-10:45 Intermission—Refreshments.

B. C. H. HARVEY, M.D., *Presiding*

- 10:45-11:15 Poliomyelitis.  
Dr. Levinson.
- 11:15-11:45 Brucellosis.  
Dr. Spink.
- 11:45-12:45 Methods of Diagnosis in Virus Diseases.  
Dr. Francis.
- 12:45- 1:15 Tularemia.  
Dr. Spink.
- 1:15- 2:15 Luncheon.

Thursday, November 2.

*Infectious Diseases (Continued)*

ROBERT S. BERGHOFF, M.D., F.A.C.P., *Presiding*

P.M. Session

- 2:15- 2:45 Review of the Status of the Treatment of *Pneumococcus Pneumonia*.  
Dr. Kelly.  
2:45- 3:15 Epidemics of Acute Respiratory Infections due to Hemolytic Streptococci and Their Relation to Rheumatic Fever.  
Dr. Spink.

*Chemotherapy*

- 3:15- 3:45 Present Status of Sulfonamide Therapy.  
Dr. Volini  
3:45- 4:15 Penicillin Therapy.  
Dr. Spink.  
4:15- 4:30 Intermission—Refreshments.  
4:30- 5:15 The Treatment of Medical and Surgical Infections with Penicillin.  
Lt. Col. Queen.  
5:15- 5:45 Treatment of Meningococcus Meningitis with Penicillin.  
Capt. McCarthy.

Friday, November 3.

*Chemotherapy (Continued)*

NEWELL C. GILBERT, M.D., *Presiding*

A.M. Session

- 8:00- 8:30 Pitfalls and Safeguards in Sulfonamide Therapy.  
Dr. Rhoads.  
8:30- 9:00 The Mode of Action of Penicillin in Meningococcal and Gonococcal Infections.  
Dr. Miller.  
9:00- 9:30 Toxic Reactions from Sulfonamide Therapy.  
Dr. Blankenhorn.

*Hematology*

- 9:30-10:00 The Differential Diagnosis and Treatment of Non-Hemolytic Anemias Resistant to Liver and Iron.  
Dr. Doan.  
10:00-10:30 Clinical Value of Sternal Puncture.  
Dr. Limarzi.  
10:30-10:45 Intermission—Refreshments.  
10:45-11:15 The Hemolytic Anemias.  
Dr. Doan.  
11:15-11:45 Diagnosis and Treatment of Leukemia.  
Dr. Alt.  
11:45-12:15 Indications and Contraindications for the Use of Radioactive Phosphorus Therapy (P 32) in Hematologic States.  
Dr. C. V. Moore, Jr.  
12:15-12:45 Infectious Mononucleosis.  
Dr. Isaacs.  
12:45- 1:15 The Significance of Splenomegaly.  
Dr. Alt.  
1:15- 2:15 Luncheon.

Friday, November 3.

*Hematology (Continued)*

WILLARD O. THOMPSON, M.D., F.A.C.P., *Presiding*

P.M. Session

- 2:15- 2:45 The Present Status of Transfusions and Blood Substitutes.  
Dr. Doan.
- 2:45- 3:15 The Rh Factor.  
Dr. Davidsoln.
- 3:15- 3:45 Prothrombin and Its Relation to Bleeding States.  
Dr. Quick.
- 3:45- 4:15 The Pathologic Physiology of Hemorrhagic Diseases.  
Dr. C. V. Moore, Jr.
- 4:15- 4:30 Intermission—Refreshments.
- 4:30- 5:00 The Rôle of the Spleen in Clinico-Pathologic States.  
Dr. Doan.
- 5:00- 5:30 Non-Tropical Sprue.  
Dr. C. V. Moore, Jr.

Saturday, November 4, 1944.

REGIONAL MEETING

OF THE

AMERICAN COLLEGE OF PHYSICIANS

DRAKE HOTEL

East Lake Shore Drive and North Michigan Avenue

PRELIMINARY PROGRAM \*

Morning Session

*Gold Coast Room*

- 9:00-12:30 Hormones of the Adrenal Cortex.  
Dr. Kendall.
- The Diagnosis of Beriberi Heart Disease.  
Dr. Blankenhorn.
- (Title to be announced later.)  
Vice Admiral McIntire (or envoy).
- New Conceptions in the Therapeutic Use of Exercise.  
Major Soto-Hall.
- The Treatment of Medical and Surgical Infections with Penicillin.  
Lt. Col. Queen.
- Penicillin Therapy at the University of Minnesota Hospitals, 1942-44.  
Dr. Spink.

Afternoon Session

*Ballroom*

- 2:00- 5:00 Rheumatic Fever.  
Col. Allen.
- Medical Treatment of Hyperthyroidism, with Special Reference to  
Thiouracil.  
Dr. Astwood.

\* The final and complete program of the Regional Meeting will be mailed at a later date.

Hepatitis.

Dr. Watson.

Neuroses in the Combat Zone—Mechanism and Prognosis.

Col. Bleckwenn.

Virus Diseases.

Dr. Francis.

Cocktails, 5:30 P.M., Gold Coast Room

Dinner, 7:00 P.M., Gold Coast Room. Short and informal speeches by various distinguished guests.

## COURSE NO. 6—SPECIAL MEDICINE

(December 4-15, 1944)

PHILADELPHIA INSTITUTIONS

PHILADELPHIA GENERAL HOSPITAL

34th Street below Spruce

THOMAS M. McMILLAN, M.D., F.A.C.P., *Director*

(Minimal Registration, 25; Maximal Registration, 50)

This unique program allots for approximately one-half day to the consideration of each of several special fields of medicine. It offers a short but detailed resumé in these several different specialties, and gives an opportunity to study under a faculty selected from various Philadelphia Institutions; including the University of Pennsylvania School of Medicine and Graduate School of Medicine; Jefferson Medical College of Philadelphia; Temple University School of Medicine; the Woman's Medical College of Pennsylvania; the Philadelphia General Hospital; Abington Memorial Hospital; the Children's Hospital; the Institute of the Pennsylvania Hospital; the Pennsylvania Hospital; Presbyterian Hospital; the Jewish Hospital; the Lankenau Hospital and the Department of Public Health of Philadelphia. The faculty is augmented also by several eminent teachers from other cities.

For the convenience of the registrants, a central meeting place, Philadelphia General Hospital, has been selected, rather than having classes held in each individual institution.

The concluding day, Friday, December 15, will be devoted to a Regional Meeting of the American College of Physicians for eastern Pennsylvania, New Jersey, Delaware and adjacent territory. All physicians taking this course, whether they be members of the College or not, are invited to participate in the Regional Meeting, to attend the noon-day luncheon and the evening dinner-meeting.

### OFFICERS OF INSTRUCTION

J. Marsh Alesbury, M.D., Chairman of the Philadelphia County Medical Society Committee on Maternal Welfare of the City of Philadelphia.

Frederick H. Allen, M.D., Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine.

Bernard J. Alpers, M.D., Professor of Neurology, Jefferson Medical College of Philadelphia.

- Kenneth E. Appel, M.D., F.A.C.P., Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine; Senior Psychiatrist, Institute of the Pennsylvania Hospital.
- J. P. Atkins, M.D., Associate in Broncho-esophagology, University of Pennsylvania School of Medicine.
- Theodore F. Bach, M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania Graduate School of Medicine.
- Oscar V. Batson, M.D., Professor of Anatomy, University of Pennsylvania Graduate School of Medicine.
- Joseph T. Beardwood, Jr., M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.
- Herman Beerman, M.D., Assistant Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Chief, Outpatient "B" Service, Dermatology and Syphilology, Pennsylvania Hospital.
- Moses Behrend, M.D., F.A.C.S., Associate in Surgery, Jefferson Medical College of Philadelphia; Attending Surgeon, Jewish and Mt. Sinai Hospitals; Consulting Surgeon, Department of Thoracic Surgery, Philadelphia General Hospital.
- Samuel Bellet, M.D., Instructor in Medicine, University of Pennsylvania School of Medicine; Associate in Cardiology, University of Pennsylvania Graduate School of Medicine; Assistant Clinical Professor of Medicine, Woman's Medical College of Pennsylvania; Assistant Chief, Cardiology, Philadelphia General Hospital.
- John V. Blady, M.D., Director of the Tumor Clinic, Temple University Hospital.
- Marion A. Blankenhorn, M.D., F.A.C.P., Professor of Medicine and Head of the Department, University of Cincinnati College of Medicine, Cincinnati, Ohio.
- Harry L. Bockus, M.D., F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Russell S. Boles, M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania School of Medicine; Gastro-enterologist, Bryn Mawr Hospital.
- Earl D. Bond, M.D., Director of Research, Institute of the Pennsylvania Hospital; Professor of Psychiatry and Vice Dean, University of Pennsylvania Graduate School of Medicine.
- Ralph S. Bromer, M.D., Clinical Professor of Radiology, University of Pennsylvania Graduate School of Medicine.
- Charles L. Brown, M.D., F.A.C.P., Professor of Medicine and Head of the Department of Medicine, Temple University School of Medicine.
- W. E. Burnett, M.D., Professor of Surgery, Temple University School of Medicine.
- W. Edward Chamberlain, M.D., F.A.C.P., Professor of Radiology, Temple University School of Medicine.
- A. Burton Chance, Jr., M.D., Instructor in Orthopedics, University of Pennsylvania Graduate School of Medicine.
- Robert Chobot, M.D., F.A.C.P., Assistant Professor of Clinical Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Pediatric Allergy, New York Post-Graduate Medical School and Hospital; Assistant Chief, Allergy Clinic, Roosevelt Hospital; President, American Academy of Allergy; New York, N. Y.
- Frank S. Clarke, M.D., Instructor in Radiology, University of Pennsylvania School of Medicine.
- Louis H. Clerf, M.D., F.A.C.P., Professor of Laryngology and Bronchoscopy, Jefferson Medical College of Philadelphia.
- Paul C. Colonna, M.D., F.A.C.S., Professor of Orthopedic Surgery, University of Pennsylvania School of Medicine.
- Edward S. Dillon, M.D., F.A.C.P., Associate Professor of Diseases of Metabolism, University of Pennsylvania School of Medicine and Graduate School of Medicine; Chief, Metabolic Division, Philadelphia General Hospital.



- Charles W. Dunn, M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania Graduate School of Medicine; Endocrinologist, Abington Memorial Hospital.
- Thomas M. Durant, M.D., F.A.C.P., Associate Professor of Internal Medicine, Temple University School of Medicine.
- W. Wallace Dyer, M.D., F.A.C.P., Instructor in Medicine, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Assistant Chief in Medicine, Philadelphia General Hospital; Physician, Diabetic Outpatient Department, and Staff, Bryn Mawr Hospital.
- Mary H. Easby, M.D., F.A.C.P., Associate in Cardiology, University of Pennsylvania Graduate School of Medicine; Chief in Medicine and Chief of Cardiac Clinic, Woman's Hospital.
- K. O'Shea Elsom, M.D., Associate in Medicine, University of Pennsylvania School of Medicine.
- Gilson C. Engel, M.D., F.A.C.S., Chief, Surgical Service "B", Lankenau Hospital; Assistant Professor of Surgery, University of Pennsylvania Graduate School of Medicine.
- William H. Erb, M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania School of Medicine.
- Lowell A. Erf, M.D., F.A.C.P., Associate in Medicine, Assistant Director of the Division of Hematology, and Director of the Transfusion Plasma Unit, Jefferson Medical College of Philadelphia.
- George E. Farrar, M.D., F.A.C.P., Associate Professor of Internal Medicine, Temple University School of Medicine.
- John T. Farrell, Jr., M.D., F.A.C.P., Clinical Professor of Radiology, University of Pennsylvania Graduate School of Medicine.
- Harriet Felton, M.D., Assistant Instructor in Pediatrics, University of Pennsylvania School of Medicine.
- Harrison F. Flippin, M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.
- George D. Gammon, M.D., F.A.C.P., Associate Professor of Clinical Neurology and Acting Head of the Department of Neurology, University of Pennsylvania School of Medicine.
- Leslie N. Gay, M.D., F.A.C.P., Associate in Medicine, Johns Hopkins University School of Medicine; Chief, Protein Clinic, Johns Hopkins Hospital; Baltimore, Md.
- Francis C. Grant, M.D., F.A.C.S., Professor of Neurosurgery, University of Pennsylvania Graduate School of Medicine.
- J. Q. Griffith, Jr., M.D., F.A.C.P., Associate in Medicine and A. Atwater Kent Fellow in Medicine, University of Pennsylvania School of Medicine.
- Paul Gyorgy, M.D., Assistant Research Professor of Pediatrics, University of Pennsylvania School of Medicine.
- Samuel B. Hadden, M.D., F.A.C.P., Associate Professor of Neurology, University of Pennsylvania School of Medicine; Visiting Psychiatrist, Philadelphia General Hospital; Neuropsychiatrist, Presbyterian Hospital.
- Alice Hamilton, M.D., Consultant, Bureau of Standards, U. S. Department of Labor (formerly Professor of Industrial Toxicology, Harvard School of Hygiene).
- Gertrude S. Henle, M.D., Instructor in Pediatrics, University of Pennsylvania School of Medicine.
- Werner Henle, M.D., Assistant Professor of Bacteriology in Pediatrics, University of Pennsylvania School of Medicine.
- Herman E. Hilleboe, M.D., Medical Director, Chief of Tuberculosis Control Division, U. S. Public Health Service, Washington, D. C.
- Joseph F. Hughes, Lt. Comdr., (MC), USNR, U. S. Naval Hospital, Philadelphia; Director of the Laboratories of the Institute of the Pennsylvania Hospital; Neurophysiologist, University of Pennsylvania School of Medicine.

Norman R. Ingraham, Jr., M.D., Chief, Division of Venereal Disease Control, Philadelphia Department of Public Health; Assistant Professor of Dermatology and Syphilology, University of Pennsylvania School of Medicine; Chief, Syphilis Clinic, and Consultant, Philadelphia General Hospital.

Harold W. Jones, M.D., F.A.C.P., Thomas Drake Cardeza Professor of Clinical Medicine and Hematology, Jefferson Medical College of Philadelphia; Director, Charlotte Drake Cardeza Foundation and Laboratories of the Division of Hematology.

Joseph V. Klauder, M.D., Associate Professor of Dermatology and Syphilology, University of Pennsylvania Graduate School of Medicine; Director, Ocular Syphilis Clinic, Wills Hospital.

Paul Klemperer, M.D., Pathologist, Mt. Sinai Hospital, New York, N. Y.

John A. Kolmer, M.D., F.A.C.P., Professor of Medicine, Temple University School of Medicine; Director, Research Institute of Cutaneous Medicine; Consultant in Serology, U. S. Public Health Service.

John Lansbury, M.D., F.A.C.P., Associate Professor of Medicine, Temple University School of Medicine.

William G. Leaman, Jr., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania.

Samuel A. Loewenberg, M.D., F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College of Philadelphia; Physician, Philadelphia General Hospital.

Francis D. W. Lukens, M.D., Assistant Professor of Medicine and Director of the George S. Cox Medical Research Institute, University of Pennsylvania School of Medicine.

Elizabeth P. Maris, M.D., Instructor in Pediatrics, University of Pennsylvania School of Medicine.

Albert A. Martucci, M.D., Director of the Department of Physical Medicine, Abington Memorial Hospital.

Robert A. Matthews, M.D., Associate Professor of Psychiatry, Jefferson Medical College of Philadelphia; Psychiatrist, Institute of the Pennsylvania Hospital.

R. L. Mayock, M.D., Medical Resident, Hospital of the University of Pennsylvania.

Thomas M. McMillan, M.D., F.A.C.P., Associate Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

Franklin R. Miller, M.D., Assistant Director, Division of Hematology, and Associate Professor of Medicine, Jefferson Medical College of Philadelphia.

Merle M. Miller, M.D., F.A.C.P., Associate in Allergy, University of Pennsylvania Graduate School of Medicine; Chief of Allergy Clinic, Graduate Hospital of the University of Pennsylvania.

T. Grier Miller, M.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine.

Sarah I. Morris, M.D., F.A.C.P., Professor of Preventive Medicine, Woman's Medical College of Pennsylvania.

F. L. Munro, Ph.D., Research Chemist, Division of Hematology, Jefferson Medical College and Hospital.

Muriel P. Munro, Ph.D., Research Chemist, Division of Hematology, Jefferson Medical College and Hospital.

Meyer Naide, M.D., Instructor in Medicine, University of Pennsylvania School of Medicine.

John R. Neefe, Capt., (MC), AUS, Assistant Instructor in Medicine, University of Pennsylvania School of Medicine.

Waldo E. Nelson, M.D., Professor of Pediatrics, Temple University School of Medicine.

Josef B. Nylin, M.D., Associate in Physiotherapy, University of Pennsylvania School of Medicine.

- A. M. Ornsteen, M.D., F.A.C.P., Assistant Professor of Neurology, University of Pennsylvania School of Medicine; Neurologist, Hospital of the University of Pennsylvania, Philadelphia General and Jewish Hospitals.
- Harold D. Palmer, M.D., F.A.C.P., Professor of Psychiatry, Woman's Medical College of Pennsylvania; Associate Professor of Psychiatry, University of Pennsylvania School of Medicine; Senior Psychiatrist, Institute of the Pennsylvania Hospital.
- Ethel G. Peirce, M.D., Assistant Visiting Physician, Service of Rheumatoid Diseases, Abington Memorial Hospital.
- Ralph Pemberton, M.D., F.A.C.P., Professor of Medicine, University of Pennsylvania Graduate School of Medicine; National Consultant in Rheumatism and Arthritis, War-Time Graduate Medical Meetings.
- Eugene P. Pendergrass, M.D., F.A.C.P., Professor of Radiology, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Director, Department of Radiology, Hospital of the University of Pennsylvania.
- William Harvey Perkins, M.D., F.A.C.P., Dean and Professor of Preventive Medicine, Jefferson Medical College of Philadelphia.
- George Morris Piersol, M.D., F.A.C.P., Director, Center for Research and Instruction in Physical Medicine, University of Pennsylvania.
- Alison H. Price, M.D., Assistant Demonstrator in Medicine, Jefferson Medical College of Philadelphia.
- Milton Rapoport, M.D., Associate in Pediatrics, University of Pennsylvania School of Medicine.
- Rufus S. Reeves, M.D., F.A.C.P., Director, Philadelphia Department of Public Health.
- Horace Reider, M.D., Chief Medical Resident, Bryn Mawr Hospital.
- Hobart A. Reimann, M.D., Magee Professor of Practice of Medicine and Clinical Medicine, Jefferson Medical College of Philadelphia.
- Stanley P. Reimann, M.D., F.A.C.P., Associate Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine; Pathologist and Director of Research Institute, Lankenau Hospital.
- John G. Reinhold, Ph.D., Principal Biochemist, Philadelphia General Hospital.
- Edward Rose, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine.
- Leonard G. Rowntree, M.D., F.A.C.P., Colonel, (MC), AUS, Director, Philadelphia Institute for Medical Research; Chief of Medical Division, Selective Service, Washington, D. C.
- Mitchell I. Rubin, M.D., Associate Professor of Clinical Pediatrics, University of Pennsylvania School of Medicine.
- David A. Sampson, M.D., Associate in Radiology, University of Pennsylvania Graduate School of Medicine.
- William G. Sawitz, M.D., Assistant Professor of Parasitology, Jefferson Medical College of Philadelphia.
- William H. Schmidt, M.D., Director of the Department of Physical Medicine, Jefferson Medical College of Philadelphia.
- Truman G. Schnabel, M.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine; Physician, Philadelphia General and Presbyterian Hospitals.
- Mildred W. Schram, Ph.D., Secretary, International Cancer Research Foundation.
- C. Wesler Scull, Ph.D., Instructor in Chemistry (Assigned to Medicine), University of Pennsylvania Graduate School of Medicine.
- Murray J. Shear, Ph.D., Biochemist, National Cancer Institute, Bethesda, Md.
- Will Cook Spain, M.D., F.A.C.P., Clinical Professor of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Allergy Clinic, New York Post-Graduate Medical School and Hospital; New York, N. Y.

- John H. Stokes, M.D., Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Director, Institute for the Control of Syphilis, University of Pennsylvania.
- Joseph Stokes, Jr. M.D., William H. Bennett Professor of Pediatrics, University of Pennsylvania School of Medicine.
- John Stouffer, M.D., Director, Psychopathic Department, Philadelphia General Hospital.
- Edward A. Strecker, M.D., F.A.C.P., Professor of Psychiatry, University of Pennsylvania School of Medicine; Consultant-in-Chief, Institute of the Pennsylvania Hospital; Special Consultant in Psychiatry to the Surgeon General of the Navy and to the Secretary of War for the Army and the Army Air Forces.
- William D. Stroud, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine; Cardiologist, Pennsylvania Hospital; Cardiologist and Director of Heart Station, Bryn Mawr Hospital; Physician-in-Chief, Cardiovascular Service, Abington Memorial Hospital.
- Paul C. Swenson, M.D., Professor of Radiology, Jefferson Medical College of Philadelphia.
- Leandro M. Tocantins, M.D., Assistant Director, Division of Hematology, and Associate Professor of Medicine, Jefferson Medical College of Philadelphia.
- James G. Townsend, M.D., Chief, Industrial Hygiene Division, U. S. Public Health Service, Bethesda, Md.
- Louis N. Tuft, M.D., Assistant Professor of Medicine and Chief of Allergy Clinic, Temple University School of Medicine.
- Henry J. Tumen, M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.
- D. L. Turner, Ph.D., Associate in Chemistry and Research Chemist to the Division of Hematology, Jefferson Medical College and Hospital.
- Elizabeth M. Turner, Ph.D., Research Chemist to the Division of Hematology, Jefferson Medical College and Hospital.
- Louis H. Twyeffort, M.D., Instructor in Psychiatry, University of Pennsylvania School of Medicine.
- Jacob H. Vastine, M.D., Professor of Radiology, Woman's Medical College of Pennsylvania.
- C. Richard Walmer, M.D., Westinghouse Electric and Mfg. Co.
- Matthew Walzer, M.D., Associate in Medicine, Cornell University Medical College; Attending in Allergy and Chief of Allergy Clinic, Jewish Hospital, Brooklyn, N. Y.
- Virgene Wammock, M.D., Assistant Director, Institute for the Control of Syphilis, University of Pennsylvania.
- W. L. White, M.D., Harrison Fellow in Surgery, University of Pennsylvania School of Medicine.
- Bernard P. Widmann, M.D., Professor of Radiology, University of Pennsylvania Graduate School of Medicine.
- DeForest P. Willard, M.D., Professor of Orthopedics, University of Pennsylvania Graduate School of Medicine.
- N. W. Winkelman, M.D., Professor of Neuropathology, University of Pennsylvania Graduate School of Medicine; Medical Director, Philadelphia Psychiatric Hospital.
- Thomas H. Wright, M.D., Instructor in Psychiatry, University of Pennsylvania School of Medicine; Clinical Director, Department for Mental and Nervous Diseases, Pennsylvania Hospital.
- H. A. Zintel, M.D., Instructor in Surgery, University of Pennsylvania School of Medicine.

## OUTLINE OF COURSE

Monday, December 4.

*Gastro-enterology*T. GRIER MILLER, M.D., F.A.C.P., *In Charge*

## A.M. Session

- 9:00-12:00
1. Etiology and Pathogenesis of Cirrhosis of the Liver.  
Dr. Tumen.
  2. Management of Cirrhosis of the Liver (Clinic).  
Dr. Brown.
  3. Some Studies on Hepatitis in Volunteers.  
Drs. Neefe and Reinhold.
  4. Emotional Aspects of Gastrointestinal Disease.  
Dr. Twyeffort.
  5. The Non-Surgical Abdomen (Clinic).  
Dr. Schnabel.
  6. Present Status of Regional Ileitis (Clinic).  
Dr. Bockus.
  7. Peptic Ulcer (Clinic).  
Dr. Boles.

Monday, December 4.

*Chemotherapy*HARRISON F. FLIPPIN, M.D., F.A.C.P., *In Charge*

## P.M. Session

2:00- 5:00 Panel Discussion: Chemotherapy.

1. Clinical Significance of Sulfamerazine Blood and Spinal Fluid Levels.  
Dr. Reinhold.
2. Local Use of Sulfonamides and Penicillin in Surgical Infections.  
Dr. Zintel.
3. Local Use of Penicillin in Bronchopulmonary Infections.  
Dr. Atkins.
4. Prophylactic Use of Penicillin in Chest Surgery.  
Dr. Burnett.
5. Treatment of Empyema and Meningitis with Penicillin.  
Dr. White.
6. Subacute Bacterial Endocarditis Treated with Penicillin.  
Dr. Mayock.
7. Para-aminohippuric Acid—Clinical Studies.  
Dr. Flippin.

Tuesday, December 5.

*Pediatrics*JOSEPH STOKES, JR., M.D., *In Charge*

## A.M. Session

- 9:00-12:00
1. The Influence of Sulfonamide Therapy on the Course of Acute Glomerulonephritis.  
Drs. Rubin and Rapoport.

2. The Present Status of Methods of Preventing Epidemic Influenza.  
Drs. Werner Henle, Gertrude Henle and Stokes.
3. A Reliable Skin Test for Determination of Susceptibility to Pertussis.  
Dr. Felton.
4. Why and How the Proper Prevention of Psychoneuroses Starts in Childhood.  
Dr. Allen.
5. Nutritional Factors in Ectoparasitic Infections with Special Reference to Infestation with Lice.  
Dr. Gyorgy.
6. The Value of Susceptibility Tests for Mumps.  
Dr. Maris.

Tuesday, December 5.

*Vitamin Deficiency*

THOMAS M. DURANT, M.D., F.A.C.P., *In Charge*

P.M. Session

- 2:00- 5:00
1. Ascorbic Acid.  
Dr. Durant.
  2. Vitamin D.  
Dr. Nelson.
  3. Vitamin K.  
Dr. Farrar.
  4. Thiamin.  
Dr. Elsom.
  5. Pellagra.  
Dr. Blankenhorn.

Wednesday, December 6.

*Heart Disease*

WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., *In Charge*

A.M. Session

- 9:00-12:00
1. Treatment of Cardiac Emergencies.  
Dr. Bellet.
  2. Congestive Cardiac Failure.  
Dr. Leaman.
  3. Peripheral Failure.  
Dr. Durant.
  4. Hypertension.  
Dr. Griffith.
  5. Treatment of Acute Rheumatic Carditis.  
Dr. Easby.
  6. Coronary Artery Disease.  
Dr. Stroud.

Wednesday, December 6.

*Metabolic Diseases*

EDWARD S. DILLON, M.D., F.A.C.P., *In Charge*

P.M. Session.

- 2:00- 5:00
1. Pathogenesis of Diabetes Mellitus.  
Dr. Lukens.

2. Surgical Aspects of Diabetic Gangrene.  
Dr. Erb.
3. The Standardization of Diabetes Mellitus by Diet and Insulin.  
Dr. Beardwood.
4. Biochemical Aspects of Diabetic Coma.  
Dr. Reinhold.
5. The Use of Plasma in the Treatment of Diabetic Coma.  
Drs. Dyer and Reider.
6. Frequent Errors in the Diagnosis of Diabetes Mellitus.  
Dr. Dillon.

Thursday, December 7.

*Arthritis and Related Conditions*

RALPH PEMBERTON, M.D., F.A.C.P., *In Charge*

A.M. Session

9:00-12:00

*Symposium*

1. Statistical Factors.
2. Pathology.
3. Physiologic Disturbances Involved.
4. Clinical Presentation of Cases, with Emphasis on Diagnostic Methods and Treatment.
5. Round Table Discussion.  
Drs. Pemberton, Bach, Scull and Peirce.

Thursday, December 7.

*Physical Medicine*

GEORGE MORRIS PIERSON, M.D., F.A.C.P., *In Charge*

P.M. Session

- |      |   |
|------|---|
| 2:00 | The Present Obligations and Opportunities of Physical Medicine.<br>Dr. Piersol.   |
| 2:20 | Rôle of Physical Medicine in the Problem of Low Back Pain.<br>Dr. Colonna.  |
| 2:40 | Physiotherapy in the Control of Neuromuscular Pain.<br>Dr. Martucci.  |
| 3:00 | Nerve Palsies, Diagnosis and Prognosis (Moving Pictures).<br>Dr. Batson.  |
| 3:20 | The Influence of Posture on Disease.<br>Dr. Schmidt.  |
| 3:40 | Diathermy: Its Uses and Abuses.<br>Dr. Nylin.   |
| 4:00 | Value of Physical Therapy in Peripheral Vascular Disease.<br>Dr. Naide.   |
| 4:20 | Physical Medicine in the Management of Poliomyelitis.<br>(a) Modern Treatment of the Acute Stage.<br>Dr. Chance.<br>(b) The Rôle of the Techniques of Physical Medicine in the Chronic Stage.<br>Dr. Willard. |

Friday, December 8.

*Hematology*

HAROLD W. JONES, M.D., F.A.C.P., *In Charge*

A.M. Session

- 9:00-12:00
1. Treatment of Polycythemia.  
Dr. Erf.
  2. Observations on the Anticephalin Activity of Normal and Hemophilic Plasmas.  
Dr. Tocantins.
  3. The Influence of Myeloid and Lymphoid Stimulating Substances on Two Mouse Tumors.  
Dr. Franklin R. Miller.
  4. Electrophoretic Separation of Factors Involved in Blood Coagulation.  
Dr. Muriel P. Munro.
  5. The Chemistry of Myeloid and Lymphoid Stimulating Substances.  
Dr. D. L. Turner.
  6. Properties of an Anti-Coagulant Present in the Blood of a Hemophiliac.  
Dr. F. L. Munro.
  7. Cellular Infiltrations of Organs of Guinea Pigs that Receive Extracts of Livers and Spleens of Patients Dead with Leukemia.  
Dr. Erf.
  8. Plasma Anticephalin Activity in Hemorrhagic and Thrombotic Disorders.  
Dr. Tocantins.
  9. The Influence of Myeloid and Lymphoid Stimulating Substances on Tissue Culture of Fibroblasts.  
Dr. Elizabeth M. Turner.
  10. Ultraviolet-irradiated Blood Transfusion as a Therapeutic Measure.  
Dr. Jones.

Friday, December 8.

*Allergy*

MERLE M. MILLER, M.D., F.A.C.P., *In Charge*

P.M. Session

- 2:00- 2:20 Laboratory Procedures in the Diagnosis of Allergic Diseases.  
Skin Testing.  
Dr. Tuft.
- 2:20- 3:00 Pathology of Bronchial Asthma.  
Dr. Klemperer.
- 3:00- 3:30 Diagnosis and Treatment of Bronchial Asthma.  
Dr. Gay.
- 3:30- 4:00 Seasonal Pollinosis. Diagnosis and Treatment.  
Dr. Walzer.
- 4:00- 4:20 Allergy in Children. Rôle of Heredity.  
Dr. Chobot.
- 4:20- 4:40 Extracts: Methods of Preparation and Standardization.  
Dr. Spain.
- 4:40- 5:00 Demonstration of Skin Testing. Passive Transfer.  
Dr. Miller.



Saturday, December 9.

*Acute Infectious Diseases*

HOBART A. REIMANN, M.D., *In Charge*

A.M. Session

- 9:00-12:00 1. Penicillin in Meningitis.  
Dr. Price.  
2. Acute Infectious Diarrheal Diseases.  
Dr. Reimann.  
3. Host Types in Tuberculosis Infections.  
Dr. Perkins.  
4. Malaria.  
Dr. Sawitz.

Monday, December 11.

THE BROAD ASPECTS OF PUBLIC HEALTH

RUFUS S. REEVES, M.D., F.A.C.P., *In Charge*

A.M. Session

- 9:00 Public Health Aspects of Maternal and Child Welfare.  
Dr. Alesbury.  
9:30 Rehabilitation Problem of the Neuro-psychiatric Service Men.  
Dr. Strecker.  
10:00 Rheumatic Fever from the Standpoint of Public Health.  
Dr. Stroud.  
10:30 Newer Techniques in Tuberculosis Control.  
Dr. Hilleboe.  
11:00 Recess.  
11:15 Round Table Discussion.

Monday, December 11.

*Industrial Medicine*

SARAH I. MORRIS, M.D., F.A.C.P., *In Charge*

P.M. Session

- 2:00- 5:00 1. Industrial Medicine's Challenge to the General Practitioner.  
Dr. Townsend.  
2. Various Types of Industrial Poisons: Their Mode of Entrance and  
Action.  
Dr. Hamilton.  
3. The Pitfalls of Diagnoses in Lead Poisoning.  
Dr. Walmer.

Tuesday, December 12.

*Psychiatry*

HAROLD D. PALMER, M.D., F.A.C.P., *In Charge*

A.M. Session

- 9:00-12:00 1. Introductory Remarks.  
Dr. Strecker.  
2. Electroencephalographic Diagnosis.  
Dr. Hughes.

3. Electric Shock Therapy in Psychiatry.  
Dr. Wright.
4. The Problem of the Depressed Patient.  
Dr. Matthews.
5. The Rewards of Illness.  
Dr. Bond.
6. Psychotherapy in Medical Practice.  
Dr. Appel.
7. Clinical Demonstration of Psychiatric Cases.  
Dr. Stouffer.

Tuesday, December 12.

*Neurology*

A. M. ORNSTEEN, M.D., F.A.C.P., *In Charge*

P.M. Session

- 2:00- 5:00
1. Functional Traumatic Neuropsychiatric Syndromes.  
Dr. Ornsteen.
  2. The Pathogenesis of Cerebral Aneurysms.  
Dr. Alpers.
  3. The Present Status of the Intervertebral Disk.  
Dr. Grant.
  4. Penicillin Therapy for Neurosyphilis.  
Dr. Gammon.
  5. Migraine and Its Equivalents.  
Dr. Winkelman.

Wednesday, December 13.

*Endocrinology*

CHARLES W. DUNN, M.D., F.A.C.P., *In Charge*

A.M. Session

- 9:00-12:00
1. Thyroid.  
Dr. Rose.
  2. Adrenals.  
Dr. Lukens.
  3. Hypopituitary States.  
Dr. Lansbury.
  4. Hyperpituitary States.  
Dr. Loewenberg.
  5. Endocrine Disorders in Selective Service Cases.  
Dr. Rowntree.
  6. Male Hormone Therapy.  
Dr. Dunn.

Wednesday, December 13.

*Syphilis*

NORMAN R. INGRAHAM, JR., M.D., *In Charge*

P.M. Session

- 2:00
- Introductory Remarks. The War as an Impelling Influence in the Control of Syphilis.  
Dr. Ingraham.

- 2:15 The Problem of Falsely Positive and Doubtful Serologic Reactions in the Diagnosis of Syphilis (Lecture, Lantern Slide Demonstration and Discussion).  
Dr. Kolmer.
- 2:50 Blindness Caused by Syphilis with a Statement on the Present Status of Penicillin Therapy in Ocular Syphilis (Lantern Slide Demonstration and Illustrative Case Records).  
Dr. Klauder.
- 3:25 Penicillin in the Treatment of Early and Late Syphilis (Clinic and Discussion).  
Drs. John H. Stokes, Beerman and Wainmock.
- 4:20 Early Diagnosis and Non-Specific Measures in the Treatment of Neurosyphilis (Clinic and Discussion).  
Dr. Hadden.

Thursday, December 14.

### *Tumors*

STANLEY P. REIMANN, M.D., F.A.C.P., *In Charge*

#### A.M. Session

- 9:00-12:00 1. Organization and Results of Anti-Cancer Examination Clinics in Philadelphia.  
Dr. Schram.
2. Chemicals as Inciters of Malignant Growths.  
Dr. Shear.
3. Carcinoma of the Colon.  
Dr. Behrend.
4. Carcinoma of the Stomach.  
Dr. Engel.
5. Pulmonary Carcinoma.  
Dr. Clerf.
6. Carcinoma of the Mouth.  
Dr. Blady.

Thursday, December 14.

### *Roentgenology*

EUGENE P. PENDERGRASS, M.D., F.A.C.P., *In Charge*

#### P.M. Session

- 2:00- 5:00 1. The General Use of X-Rays in Obstetrics.  
Dr. Swenson.
2. Roentgenologic Consideration of Inflammatory Conditions of the Chest.  
Dr. Clarke.
3. The Roentgenology of the Upper Cervical Spine and Base of the Skull.  
Dr. Chamberlain.
4. The Roentgen Diagnosis of Gastrointestinal Conditions in Infants and Children.  
Dr. Bromer.
5. The Roentgenologic Problems of the Stomach and Duodenum.  
Dr. Widmann.
6. The Roentgenologic Problems of the Colon.  
Dr. Farrell.

7. Sialography.  
Dr. Blady.
8. Subcutaneous Urography.  
Dr. Vastine.
9. The Roentgenology of the Urinary Tract.  
Dr. Sampson.

Friday, December 15.

# REGIONAL MEETING

OF THE

AMERICAN COLLEGE OF PHYSICIANS

## *Morning Session*

WILLIAM HARVEY PERKINS, M.D., F.A.C.P., *In Charge*

JEFFERSON MEDICAL COLLEGE HOSPITAL

1025 Walnut Street

### A.M. Session

9:00-12:00 The Staff of the Jefferson Medical College and Hospital will present a program of clinics and demonstrations, details of which will be included in a special Regional Meeting Program that will be published later and placed in the hands of each registrant in advance of the opening of this course.

### P.M. Session

1:00 Buffet Luncheon.  
College Headquarters, 4200 Pine Street.

## *Afternoon General Session*

WILLIAM D. STROUD, M.D., F.A.C.P., *In Charge*

BENJAMIN FRANKLIN HOTEL

9th and Chestnut Streets

*Ballroom, Mezzanine Floor*

2:00- 5:00 A Symposium on Rheumatic Fever by eminent authorities. Detailed Program will be furnished to each registrant in advance of the opening of this course.

6:30 Cocktail Party (Betsy Ross Room) and Dinner Meeting (Grand Ballroom).

Guests will include Regents and Officers of the College, the Surgeons General, or their official envoys, of the U. S. Army, U. S. Navy and U. S. Public Health Service, and other distinguished medical men. Selected, timely, short addresses will be given by the President of the College, Dr. Ernest E. Irons, and others.

## READING LIST AND BIBLIOGRAPHY

An attempt is made to obtain reading lists for each Postgraduate Course for publication in the ANNALS OF INTERNAL MEDICINE, making these lists available to the entire membership of the College, in addition to preparing better the men who will take the courses. These lists are not to be considered as all-inclusive.

*Allergy—Course No. 4**Textbooks*

- Practice of Allergy. Warren T. Vaughan. C. V. Mosby Co., St. Louis, 1939.  
 Asthma and Hay Fever in Theory and Practice. A. F. Coca, M. Walzer and A. A. Thommen. Charles C. Thomas, Baltimore, 1931.  
 Clinical Allergy. Louis Tuft. W. B. Saunders Co., Philadelphia, 1937.  
 Occupational Diseases of the Skin. Louis Schwartz and Louis Tulipan. Lea and Febiger, Philadelphia, 1939.

*Monographs*

- Allergy. C. E. Von Pirquet. Archives of Internal Medicine 7: 259, 1911.  
 Anaphylaxis, Hypersensitiveness and Allergy. W. W. C. Topley. An Outline of Immunity, Chapter 12, p. 192. Wm. Wood Co., 1935.  
 Hypersensitiveness, Anaphylaxis, Allergy. H. Gideon Wells. The Chemical Aspects of Immunity, Chapter 9, p. 225, second edition. Chemical Catalog Co., New York, 1929.  
 Diseases of Allergy. Robert A. Cooke. Chapter 21, p. 1079, Internal Medicine. John H. Musser. Lea and Febiger, Philadelphia, 1938, third edition.  
 Diseases of Allergy. Robert A. Cooke. Page 535, A Textbook of Medicine. Russell L. Cecil. W. B. Saunders Co., Philadelphia, 1940, fifth edition.  
 Human Sensitization. Robert A. Cooke and A. Vander Veer. Journal of Immunology 1: 201, 1916.  
 Herter Lectures. H. H. Dale. Bulletin Johns Hopkins Hospital 31: pps. 257, 310, 373, 1920.  
 Anaphylaxis. Carl A. Dragstedt. Physiol. Rev. 21: 563, 1941.  
 Histamine and Anaphylaxis. W. Feldberg. Annual Review of Physiology, March 1941.

*Articles**Immunological Basis of Sensitization*

- Horse Asthma Following Blood Transfusion. M. A. Ramirez. J. A. M. A. 73: 984, 1919.  
 Studies on the Reactions of Asthmatics and on Passive Transference of Hypersusceptibility. Arent de Besche. Am. J. Med. Sciences 166: 265, 1923.  
 Indirect Method of Testing. M. Walzer. J. Allergy 1: 231, 1930.  
 Studies in Hypersensitiveness. XXXVI. A Comparative Study of Antibodies Occurring in Anaphylaxis, Serum Disease and the Naturally Sensitive Man. Robert A. Cooke and W. C. Spain. J. Immunol. 17: 295, 1929.  
 Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals. W. B. Sherman, A. Stull and S. F. Hampton. J. Immunol. 36: 447, 1939.  
 Serological Evidence of Immunity with Co-existing Sensitization in a Type of Human Allergy. Hay Fever. R. A. Cooke, J. H. Barnard, S. Hebal and A. Stull. J. Exper. Med. 62: 773, 1935.  
 Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients. M. H. Loveless. J. Immunol. 38: 25, 1940.  
 Studies in the Transmission of Sensitization from Mother to Child in Human Beings. S. D. Bell and Z. Eriksson. J. Immunol. 20: 447, 1931.  
 The Placental Transmission of Antibodies in the Skin-Sensitive Type of Human Allergy. W. B. Sherman, S. F. Hampton and R. A. Cooke. J. Exper. Med. 72: 611, 1940.

- The Question of the Elimination of Foreign Protein (Eggwhite) in Woman's Milk. H. H. Donnelly. *J. Immunol.* 19: 15, 1930.
- The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin. E. L. Burky. *J. Allergy* 5: 466, 1934.

#### *General Clinical Allergy*

- History Taking in Allergic Diseases. F. M. Rackemann. *J. A. M. A.* 106: 976, 1936.
- Studies in Specific Hypersensitiveness. III. On Constitutional Reactions: The Dangers of the Diagnostic Cutaneous Test and Therapeutic Injection of Allergens. R. A. Cooke. *J. Immunol.* 7: 119, 1922.
- The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. F. F. Furstenberg and L. N. Gay. *Bull. Johns Hopkins Hospital* 60: 412, 1937.
- The Delayed Type of Allergic Reaction. R. A. Cooke. *Ann. Int. Med.* 3: 658, 1930.
- Treatment of Allergic Disorders with Histamine and Histaminase. H. L. Alexander. *J. Lab. & Clin. Med.* 26: 110, 1940.

#### *Asthma*

- Asthma in Children. R. A. Cooke. *J. A. M. A.* 102: 664, 1934.
- Infective Asthma. Indication of Its Allergic Nature. R. A. Cooke. *Am. J. Med. Sci.* 183: 309, 1932.
- Relation of Asthma to Sinusitis with Special Reference to the Results from Surgical Treatment. R. A. Cooke and R. C. Grove. *Arch. Int. Med.* 56: 779, 1935.
- The Pathology of Bronchial Asthma. H. L. Huber and K. K. Koessler. *Arch. Int. Med.* 30: 689, 1922.
- Effects on Heart of Long Standing Bronchial Asthma. H. L. Alexander, D. Luten and W. B. Kountz. *J. A. M. A.* 88: 882, 1927.
- Deaths from Bronchial Asthma. W. B. Kountz and H. L. Alexander. *Arch. Path.* 5: 1003, 1928.
- Studies in Specific Hypersensitiveness. IV. New Etiologic Factors in Bronchial Asthma. R. A. Cooke. *J. Immunol.* 7: 147, 1922.
- Asthma Due to a Fungus-*Alternaria*. J. G. Hopkins, R. W. Denham and B. M. Kesten. *J. A. M. A.* 94: 6, 1930.

#### *Nasal Allergies*

- Seasonal Hay Fever and Asthma Due to Molds. S. M. Feinberg. *J. A. M. A.* 107: 1861, 1936.
- Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps. R. A. Kern. *J. A. M. A.* 103: 1293, 1934.
- The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever. R. A. Cooke and A. Stull. *J. Allergy* 4: 87, 1933.
- New Plan for Applying Specific Treatment of Pollen Hay Fever (Perennial Treatment): Aaron Brown. *J. Immunol.* 13: 273, 1927.
- The Relative Merits of Seasonal and Perennial Treatment of Hay Fever. A. Vander Veer. *J. Allergy* 7: 578, 1936.
- Calculating Pollen Concentration of the Air. E. C. Cocke, *J. Allergy* 8: 601, 1937.
- Evaluation of the Ragweed Hay Fever Resort Areas of North America. O. C. Durham. *J. Allergy* 8: 175, 1937.

#### *Intestinal Allergy*

- Gastrointestinal Manifestations of Allergy. R. A. Cooke. *Bull. N. Y. Acad. Med.* Second Series IX: 15, 1933.

Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy.  
W. T. Vaughan. *Rev. Gastroenterol.* 5: 1, 1938.

### *Skin Allergy*

- A Tentative Classification of Allergic Dermatoses. M. B. Sulzberger, F. Wise and J. Wolf. *J. A. M. A.* 104: 1489, 1935.
- A Critical Review of 170 Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years. A. I. Fink and L. N. Gay. *J. Allergy* 5: 615, 1934.
- Eczema. L. W. Hill. Vol. IV., Chapter 43, Brenneman's Practice of Pediatrics. W. F. Prior Co., Hagerstown, Md.
- Studies in Specific Hypersensitiveness. XXVII. Dermatitis Venenata: Toxicodendron Radicans. W. C. Spain and R. A. Cooke. *J. Immunol.* 13: 93, 1927.
- Report of the Investigation and Successful Treatment (Preventive) of Dermatitis Resulting from the Handling of Tulip Bulbs. A. H. W. Caulfeild. *J. Allergy* 8: 181, 1937.

### *Miscellaneous Allergy*

- Cerebral Symptoms Induced by Angioneurotic Edema. F. Kennedy. *Arch. Neurol. and Psychiat.* 15: 28, 1926.
- Allergic Migraine. W. T. Vaughan. *J. A. M. A.* 88: 1983, 1927.
- Food Allergy in Henoch's Purpura. H. L. Alexander and C. H. Eyermann. *Arch. Dermat. & Syph.* 16: 332, 1927.
- The Clinical Diagnosis of Periarteritis Nodosa. M. B. Cohen, B. S. Kline and A. M. Young. *J. A. M. A.* 107: 1555, 1936.
- Allergy Induced by Immunization with Tetanus Toxoid. R. A. Cooke, S. F. Hampton, W. B. Sherman and A. Stull. *J. A. M. A.* 114: 1854, 1940.
- Elimination of Horse Serum Specificity from Antitoxins. R. D. Coghill, N. Fell, M. Creighton and G. Brown. *J. Immunol.* 39: 207, 1940.
- Physical Allergy. W. W. Duke. *J. A. M. A.* 84: 736, 1925.
- Allergy in Drug Idiosyncrasy. R. A. Cooke. *J. A. M. A.* 73: 759, 1919.

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 21

OCTOBER, 1944

NUMBER 4

---

## RÔLES OF MEDICINE AND SURGERY IN THE MANAGEMENT OF BRONCHIECTASIS \*

By JOHN ALEXANDER, M.D., *Ann Arbor, Michigan*

GREAT variability in the clinical behavior of patients with bronchiectasis and the failure of many vaunted methods of treatment have led to widespread confusion concerning the management of this prevalent disease, which is encountered from early childhood to old age and which produces an appalling aggregate amount of disability.

For many years physicians and surgeons longed for the time when the curative operation of lobectomy would be safe, hoping that this would virtually solve the difficult problem of treatment. Lobectomy is now safe but, as only about half of all bronchiectasis patients are suitable for the operation, other methods of treatment, which are necessarily only palliative, must still be used for the remaining half. It is primarily because many physicians are utterly pessimistic about the effectiveness of these other methods of treatment and because of my conviction that they can often be made effective, that this article is being presented. In the course of the article I shall also discuss those various points about bronchiectasis which continue to cause confusion with regard to the etiology, diagnosis, and the medical and surgical management of the disease.

### BASIC TYPES OF BRONCHIECTASIS

From the point of view of treatment, it is obviously important that a distinction be made between (1) cases of bronchiectasis in which there is no obstruction of the larger bronchi; (2) cases in which varying degrees of obstruction of the larger bronchi exist, owing to foreign body, bronchial carcinoma or adenoma, tuberculous granulation tissue or fibrous stricture in the bronchial wall, pyogenic granulation tissue and extrabronchial pressure by enlarged lymph nodes or other tumors; (3) those relatively infrequent cases which present the characteristic symptoms of bronchiectasis but in

\* Received for publication October 25, 1943.

From the Department of Surgery, University of Michigan.



## BRONCHIECTASIS WITH AND WITHOUT ASSOCIATED PNEUMONITIS

Some cases of bronchiectasis have no associated gross pneumonitis, the roentgenograms showing no pulmonary infiltration whatever, and inspection and palpation of the affected lobe at the time of a lobectomy operation showing a soft, pink parenchyma without overlying pleural adhesions. In such cases, the surgeon might question the diagnosis of bronchiectasis in that particular lobe, if the bronchograms did not give certain evidence of the correctness of the diagnosis.

In those many cases in which suppurative pneumonitis is associated with the bronchiectases, there is great variability in the lesions and in the degree of toxicity and in other clinical manifestations. Contracting fibrous tissue with microscopic evidence of diffuse parenchymal suppuration, or gross evidence of tiny or larger parenchymal abscesses, in addition to the bronchiectases themselves, and more or less extensive pleural adhesions, are the principal lesions. Contraction of the fibrous tissue may produce areas of obstructive emphysema and cyst-like dilatations of the small bronchi, or a tension type of parenchymal abscess. Patches of emphysema and emphysema of unaffected lobes may, however, be entirely compensatory for the contraction of the affected lobe or lobes.

The cellular infiltration and the fibrous tissue in the parenchyma tend to cause the affected lobe to be firm and small. This condition is not predominantly atelectasis although, unfortunately, it is usually referred to as such, probably because the roentgenographic appearances of the two conditions are similar (including the drawing of surrounding structures toward the small lobe) and because a pure form of total lobar atelectasis (which is capable of disappearing and leaving a normal lobe) often initiates the train of events leading to bronchiectasis and a small dense fibrotic lobe (which can never again become a normal lobe). Boyd, Anspach and others have described the relationship between bronchiectasis and pure lobar atelectasis that is represented roentgenographically by a small triangular shadow.

## SYMPTOMS AND SIGNS

The symptoms and signs of bronchiectasis are cough with or without sputum or hemoptysis; scanty or abundant purulent or mucopurulent sputum that may be intermittently foul in odor; susceptibility to frequent upper respiratory or bronchial "colds" that may be so mild as to resemble a true chronic bronchitis or so severe as to be diagnosed as pneumonia; asthma-like attacks that are not due to asthma but that respond to epinephrine or ephedrine, which relieves the bronchial mucosal congestion and, consequently, the wheezing; continuous or intermittent fever, that may be trivial in amount; fatigue that may be so great as to be disabling or so little that only the patient's family recognizes it; malaise; weakness; loss of weight; night sweats; anemia; pleurisy; dyspnea and miscellaneous other symptoms and

signs. The psychological disability that the social and economic handicaps of bronchiectasis create has been ably described by Churchill and by Riggins.

There is a surprising variability in the symptoms, as well as in their severity, in different cases of bronchiectasis, and also in the same patient at different times. In some patients the symptoms are so variable that the true diagnosis is not even suspected, the symptoms being attributed to undernourishment, a frail constitution, anemia, asthmatic or atypical chronic bronchitis; this is especially so in children. In other patients recurring attacks of suppurative pneumonitis are diagnosed as pneumore-unresolved pneumonia without the basic pathological condition being suspected. Even when the bronchiectatic lesions are not in the upper or lower lobe tuberculosis is often mistakenly diagnosed because of the similarity in the symptoms, especially when there is hemoptysis; there are many bronchiectatic patients in sanatoria in whom tubercle bacilli have never been found for an sputum and in whom good bronchograms have never been made.

### DIAGNOSIS

The diagnosis of bronchiectasis is suggested by the history, symptoms, physical signs and the roentgenographic and bronchoscopic findings. At two without exception, however, an absolute diagnosis depends upon iodized bronchograms. Physical examination of the lungs yields such valuable findings that its chief value is in the localization of some pulmonary abnormality. In a considerable number of cases in which there is no associated pneumonitis, there may be a complete absence of abnormal physical findings; râles and some alteration in breath sounds may be demonstrable on a subsequent examination. Patients having the parenchymal cellular infiltration and fibrosis of suppurative pneumonitis have the physical findings that such lesions produce. It is an interesting fact, however, that a thoracoevacuation (by postural drainage or bronchoscopy) of secretions that have been choking the large and small bronchi may cause an immediate striking change in the physical findings. Dullness, distant breath sounds with or no post-tussic râles, which are the usual findings when the bronchi are choked with secretions, become, respectively, resonance or slight dullness, clear breath sounds with many crepitant râles and rhonchi after the previously choked bronchopulmonary areas have become aerated.

### ROENTGENOLOGY

Mention has already been made of those occasional cases of bronchiectasis without pneumonitis in which no abnormality can be seen in the roentgenograms. In other cases peribronchial thickening is revealed by increased bronchial markings or as ring shadows. More extensive infiltration around the bronchial walls or in the parenchyma may appear as a patchy infiltration resembling bronchial pneumonia, tuberculosis, fungus disease or the congested pulmonary vessels of congestive cardiac failure. Faint linear

of fibrous tissue may be only indistinctly seen but their contraction may be manifested by retraction of the mediastinum and diaphragm and by a visible, displaced interlobar fissure. Extensive cellular infiltration and parenchymal fibrosis appear, or they may occupy an entire lobe, which is usually much replete of emphyse. When such a contracted infiltrated lobe is the left lower, its shadow may lie entirely behind the heart and be invisible in a postero-anterior roentgenogram of standard density; the shadow can be readily seen in a lateral projection roentgenogram which is not overexposed, or in an overexposed or Potter-Bucky technic postero-anterior film. The diversity of roentgenologic shadows seen in bronchiectasis is responsible for their toxic frequent misinterpretation, and for the mistaken diagnoses of tuberculosis, fungus disease, congestive cardiac failure, pneumonia, pulmonary emphysema, bronchogenic carcinoma, atelectasis, localized pleural effusion or other conditions. Andrus' article ably describes the roentgenologic findings in bronchiectasis.

obstruction  
tension

#### BRONCHOGRAMS

Iodized oil bronchograms are necessary to establish a definite diagnosis. Though the introduction of the oil into only the lower parts of the lungs, followed by the making of a postero-anterior roentgenogram, and without any preparation of the patient, may reveal the presence of bronchiectasis, this technic is so antiquated and furnishes so little information about the extent and position of the lesions, that it should be promptly discarded. A more or less routine procedure should be followed in connection with the making of bronchograms:

1. A lateral projection roentgenogram and stereoscopic, postero-anterior, standard-technic roentgenograms should be obtained before the bronchograms are made in order to learn as much as possible about whatever abnormal shadows may be present in the lungs, since prolonged retention of iodized oil in the lungs may for months or even years prevent an accurate interpretation of pulmonary shadows.

2. Virtually every patient having bronchiectasis, or suspected of having it, should have a bronchoscopic examination. Bronchoscopy alone gives accurate information about such obstructing bronchial lesions as carcinoma, foreign body, and pyogenic granulation tissue. The chemical shrinkage of the inflamed bronchial mucosa and the thorough aspiration of all secretions that can be reached with a bronchoscopic aspirator not only benefit the patient but also clear the bronchi for the reception of the iodized oil that should be introduced within the following 48 hours, postural drainages being used in the interval in order to keep the bronchi as clear as possible.

3. Iodized oil should not be introduced into the lung within three weeks following the disappearance of an attack of acute pneumonitis or any febrile episode which presumably had its origin in the pulmonary lesions. The

breaking of this rule may result in a serious, and occasionally fatal attack of acute pneumonitis.

4. Immediately after a postural drainage and after producing the same local anesthesia of the pharynx, larynx, trachea and bronchi which is used for bronchoscopy, the lipiodol should be introduced in such a way that the bronchi of all five lobes of the lungs are well coated. This may be done in two sittings, but preferably in one sitting. A series of roentgenograms must immediately be made in certain specified projections that will permit an exact differentiation not only of the bronchi of the different lobes but also of the segments of the lobes, as these findings are essential for consideration of the advisability or inadvisability of lobectomy. A technic for the introduction of the iodized oil and for the making of the roentgenograms has been described in detail by Adams and Davenport. If, for any reason, any lobar, or segment of a lobar, bronchus has not been adequately filled for an accurate interpretation of the roentgenograms, another attempt to outline the defectively filled bronchus should be made a few days later, if a lobectomy operation is being considered. Although the demonstration of bronchiectases is the primary purpose of bronchograms, the persistence of a filling defect in any bronchus proximal to the bronchi of the fourth order in two or more series of bronchograms is of the greatest clinical significance since such a filling defect indicates not only that there is a probably harmful bronchial obstruction but also that bronchiectases presumably exist in the pulmonary segment beyond the obstruction. What has just been said does not refer to the filling defects which are almost constantly present in the small bronchi distal to those bronchiectases which have been outlined by the iodized oil, because these small bronchi are not constricted but are clogged with secretions and so have no room for the oil.

When treatment, particularly lobectomy, is being discussed while bronchograms are being studied, a statement is occasionally made to the effect that the bronchiectases are too few or too poorly developed to require active treatment. I have seen many patients with such lesions who had exceptionally severe and disabling symptoms (probably because of poor bronchial drainage) and other patients with extensive, well developed bronchiectases whose symptoms were relatively mild (probably because of good bronchial drainage). I have recently seen a woman having a few slightly widened bronchi in the middle lobe; a careful study of the bronchograms, however, revealed several areas of filling defect. A well known physician had assured the patient that she had no bronchiectasis and that a winter in a sunny dry climate would cure her. When I saw her at the end of the winter there were dullness and râles over a small middle lobe and the patient was excessively fatigued, greatly underweight, had a slight afternoon elevation of temperature, moderate cough and scanty sputum. Active treatment is urgently needed by this patient in spite of the apparent innocence of the few bronchiectatic lesions shown by the bronchograms.

## PROGNOSIS

Great variability in the clinical behavior of different cases of bronchiectasis has created considerable confusion about the prognosis. Some patients, particularly those whose illness has never required treatment in a hospital, enjoy moderately good health for a great many years. Other patients, usually those who have had repeated attacks of acute pneumonitis, are seriously disabled most of the time and are likely to die within a few years after the onset of the disease. There are, of course, many gradations of illness between these extremes. The conclusion of those clinicians who have made special studies of the prognosis is that it is much worse than those who have not investigated the matter believe. In this connection the reader is referred to the articles of Perry and King; Bradshaw, Putney and Clerf; Riggins; Findlay and Graham; and Roles and Todd. A mere list of the complications (only the last few being infrequently seen) indicates the potential gravity of bronchiectasis: repeated attacks of acute suppurative pneumonitis; pulmonary abscess or gangrene; septicemia; pleural empyema; spontaneous pneumothorax; brain abscess or meningitis; repeated severe hemoptyses; pulmonary fibrosis, emphysema, cor pulmonale, myocardial degeneration, cardiac decompensation; nephritis and amyloid disease; suppurative pericarditis; suicide; arthritis, and carcinoma from metaplasia of chronically inflamed bronchial mucosa.

## TREATMENT

Elastic bronchial walls apparently may be stretched or dilated as a result of atelectasis and later resume their normal caliber with the disappearance of the atelectasis, provided infection of the bronchial walls has not occurred, destroying their elasticity. This train of events, which is probably rare, is generally believed to represent the only instance in which bronchiectases disappear, with or without the aid of treatment. Only a few cases have been reported in which bronchiectases that were infected and had produced the clinical picture of bronchiectasis, later disappeared.

The aim of treatment, therefore, is either to reduce, as far as possible, the ill effects of the permanent lesions by nonsurgical means, or to remove completely the lesions by the operation of lobectomy. Since nonsurgical treatment is necessarily only palliative, and since even a patient whose condition has been greatly improved by it, is constantly in danger of suffering a relapse, lobectomy is obviously the only form of treatment that can produce a cure.

Lobectomy is, without question, overwhelmingly the treatment of choice for those patients (1) whose age, cardiorespiratory functional reserve and general condition are suitable; (2) whose lesions are restricted to one lobe, or to the right lower and middle lobes, or to the left lower and lingular ("left middle") lobes or, in some cases, to all the lobes of one lung (total pneumonectomy) or to one lobe of each lung or to two lobes of one lung and one

lobe of the other lung (bilateral lobectomy); (3) who have failed to attain a satisfactorily stable condition of improvement from nonsurgical treatment. In view of the potential gravity of bronchiectasis, because of the ever present danger of some serious complication, the validity of the third condition, just mentioned, is subject to question, especially in young patients with lesions in only the lower lobe, or lower and middle lobes, of one lung. The risk of lobectomy in children as young as five years of age is apparently less than average, and in adults in the fourth and even fifth decades of life not much greater than average. Special additional reasons for performing lobectomy in childhood are that the dangers of bronchiectasis are particularly great then and that the removal of the lesions makes probable a normally long life of health, in place of a probable short life of varying degrees of illness and disability.

The factors that determine a particular patient's suitability or unsuitability for lobectomy are so many and complex in their inter-relationships that unqualified indications for the operation cannot be given. Obviously the indications are far broader at present, when the surgical mortality\* is approximately only 5 per cent in certain clinics, than in 1932 when Lilienthal reported a surgical mortality rate of 62.5 per cent for his 40 cases of partial or complete lobectomy. The present mortality rate varies rather widely from clinic to clinic. Dolley and Jones in 1939 collected 549 cases of lobectomy for bronchiectasis in which there had been 127 (23 per cent) deaths, but these 549 cases include early series of cases. The death rate in the cases collected after 1929 was about 18 per cent. In 1939 Bradshaw, Chodoff and Deardorff reported three deaths in 30 cases, or 9.6 per cent (sic). Edwards in 1939 reported 20 (12.5 per cent) hospital deaths in 166 lobectomy operations on 160 patients, and six later deaths, but in his last 54 cases there were only two deaths (3.7 per cent). Perry and King in 1940 reported that Churchill had had only four deaths (3.3 per cent) in 122 lobectomy operations on 116 patients. Alexander and O'Rourke report three deaths (4.3 per cent) directly connected with operation, and two late deaths (2.9 per cent) in 70 consecutive patients operated upon by Alexander or Haight. One of the late deaths occurred six months after operation from a fulminating pneumonia in a patient who developed a pulmonary abscess three months after operation; the other late death occurred five months after operation from a bacteremia which arose three days after the changing of an empyema drainage tube three months after operation in a patient who was doing well except for a persisting small empyema pocket.

The indications for lobectomy may become further extended in certain cases of multiple-lobe bronchiectasis by the wider application of Churchill and Belsey's suggestion that in certain cases only affected segments of lobes be removed. This principle has been applied for a number of years in the

\* These figures express, with a few exceptions, the rate for the removal of the lower lobe, or lower and middle lobes, of one lung. The rate for bilateral lobectomy is considerably higher.

removal of the lingular segment of the left upper lobe, which is technically simpler and safer than for any other lobar segment.

Being a surgeon who has performed lobectomy operations in increasing numbers during the last 15 years and having seen many patients transformed from a state of prolonged wretched ill health to perfect health, I am as aware as anyone could be of the value of lobectomy. But I also know that there are a great many bronchiectasis patients whose cases are not, for various good reasons, suitable for lobectomy, and I know from long experience that a majority of these patients, although unfortunately not all, can be greatly helped by the faithful use of nonsurgical measures. These measures cannot cure the disease and only rarely do they bring about even a temporary complete disappearance of symptoms, but they frequently so greatly improve the symptoms that they become minor annoyances rather than the cause of distressing disability. I am, therefore, unable to understand the pessimism of Riggins and of Lisa and Rosenblatt about nonsurgical treatment for the relief of those patients for whom the curative operation of lobectomy cannot be performed. Lisa and Rosenblatt state in their 1943 book on bronchiectasis that "some palliative procedures have been retained chiefly as adjunct procedures to lobectomy," and in the summary of the book not one word is said about nonsurgical treatment. Many readers will infer that the authors of this book believe that lobectomy is suitable for practically all bronchiectasis patients. Unfortunately many are not suitable and these should receive medical treatment.

Postural drainage is the most valuable of the nonsurgical therapeutic measures and, yet, it is usually used inefficiently. Its aim is to improve bronchial drainage, thereby lessening toxic absorption from retained bronchopulmonary secretions and reducing infection in the bronchi and lung. The maximal good effect would be obtained if all free secretions could be drained away as rapidly as they form; some clinicians have attempted to do this by keeping their patients continuously in bed for several weeks or months, the foot of the bed being elevated about 15 inches. Almost as effective, and more practical for patients who need not remain in bed, is the use of postural drainage every two hours \* from the time of awakening until bed time (and at night, if the patient should awaken), the schedule being so adjusted that no postural drainage comes within an hour after a meal. Postural drainage should be carried out by the patient's leaning over the edge of a bed or table sufficiently high to cause his torso to be inverted perpendicularly when his hands are resting on the floor. The taking of half a dozen deep breaths before each half dozen hard coughs loosens the secretions better for expectoration and aerates the affected portion of the lung better than if the inversion and coughing are alone relied upon. Cycles of deep breathing and hard coughing should be repeated until the patient feels that no more secre-

\* After two or three weeks, if the secretions have been greatly reduced, the interval between drainages may properly be lengthened to three or even four hours.

tions can be loosened for expectoration. The duration of a postural drainage should not be prescribed in minutes.

Patients who are not accustomed to an inverted posture may at first become dizzy and need to be helped up before the drainage has been completed. Patients who have full-time jobs may be unable to find a high table in a non-public place where postural drainage can be carried out during working hours. Bending as far forward as possible at the hips in a lavatory (the knees being bent, the hips high and the head close to the floor) serves as a reasonably satisfactory substitute for the regular position. Although the inverted position that has been described is the one that produces the best drainage in most patients, some learn from trial that other postures are more effective in their particular cases, such as lying upon the back, the face or one or the other side, with or without the foot of the bed elevated. These modified postures are suitable for patients who are too ill or feeble for the rather strenuous inverted posture. Occasionally, patients find that expectoration is freest in the sitting or standing position, but that the preliminary inverted posture loosens the secretions for ready expectoration. A bronchoscopy carried out immediately after a postural drainage determines the relative number of retained secretions and, therefore, gives an indication of the probable effectiveness of postural drainage.

Every bronchiectatic patient should have at least one bronchoscopic examination, not only because some otherwise undetectable, important intra-bronchial lesion may be discovered but also because the aspiration of secretions and the chemical shrinkage of the bronchial mucosa often bring about improvement in the symptoms, which in occasional cases (notably in children, and also in adults) is astonishingly great. Bronchoscopy is also of great value in preventing the development of bronchiectasis in *early* cases of pneumonitis or "unresolved pneumonia." The ordinary bronchoscopic treatment, in which a few of the secretions are aspirated and in which the mucosa is treated for only a few moments, is of little value. An effective treatment, which should be immediately preceded by a postural drainage and which may occupy from 15 to 30 minutes, requires (1) that the bronchi containing secretions should be repeatedly aspirated until all free secretions have been removed, both before and after the mucosa has been shrunk and the patient has repeatedly coughed on command, and (2) that equal parts of 2 per cent pantocaine and 1 to 1,000 epinephrine solutions, or other shrinking drugs, be directly applied, step by step, to all parts of the mucosa that are swollen, and that an excess of the solution in the gauze pledgets be squeezed into those bronchi of the affected parts of the lung that are too small to be directly reached by the pledgets, or that a small amount of the solution be injected into these bronchi.

The effect of this treatment is to empty and open the choked bronchi, most of which (including the bronchiectases themselves) are distal to the field of bronchoscopic vision. The small bronchi in the peripheral portion of the



bronchiectatic lobes cannot be reached by the bronchoscopic aspirator but they can be at least partially emptied of secretions by voluntary coughing after all secretions proximal to them have been aspirated. Air enters more and more deeply into the lung as the secretions are aspirated and coughed from the bronchopulmonary areas that had been drowned in secretions. The aëration of the peripheral portions of the affected lobes is the most important objective of bronchoscopic treatment. Aëration of the small bronchi and alveoli is the most effective means of aiding the patient to evacuate additional secretions by coughing, both during and following bronchoscopy. Deep breathing and coughing at from 15 to 60 minute intervals during waking hours for one or two days after a bronchoscopic treatment, and the faithful carrying out of postural drainages indefinitely after bronchoscopy are obviously important in maintaining aëration and maximal evacuation of secretions. Evidence that a choked portion of a lung has been drained and aërated is often furnished by the change from dullness to resonance, from distant or almost absent breath sounds to distinct breath sounds, and from few or no râles to many râles, as a result of a particularly effective bronchoscopic treatment, and sometimes as a result of only a postural drainage. The length of time during which aëration and drainage are maintained probably depends in part upon the faithfulness of the patient in carrying out the prescribed postural drainages, and in part upon whether the good effects of aëration and of whatever reduction in infection of the bronchial mucosa occurs as a result of the improved drainage predominate over a recurrence of the mucosal swelling, which presumably may occur as a secondary reaction to the drugs that were used to shrink the mucosa.

Experience has shown that in a few cases, one bronchoscopic treatment removes all the particularly distressing symptoms for an indefinite period of time. In a greater number of cases, no relief of symptoms occurs and in a very few cases the symptoms are made worse through an acute attack of pneumonitis. In a majority of patients a satisfactory improvement takes place but, in the course of a week, or several weeks or months, a relapse occurs, calling for another bronchoscopic treatment. In those patients who are indefinitely relieved by one bronchoscopic treatment, or who are not relieved at all, further treatments are obviously not indicated. In the other patients, repeated bronchoscopies are indicated at whatever intervals (five days, several weeks or months) the circumstances require. I have had no experience with bronchoscopic irrigations; from what I hear, I believe that they are, at best, no more effective than the treatment that has been described in this article and that they expose the patient to the danger of an attack of pneumonitis.

Since the primary purpose of nonsurgical treatment is to bring about the maximal evacuation of secretions, cough medicines that check the cough reflex are not only not helpful but are harmful, and measures that promote expectoration are beneficial. Such expectorants as ammonium chloride, iodides, ipecac, steam inhalations that may be medicated with benzoin or

menthol, and the inhalation of a nebulized spray of 1 to 100 dilution of epinephrine solution may prove useful if the secretions are thick and especially viscid, and if expectoration is difficult. Some clinicians recommend the therapeutic instillation of iodized oil into the affected bronchi every week or so; they say the mucosa is thereby soothed, cough, stagnation and fetor of the secretions relieved and the general condition of the patient improved. I have seen such improvement too infrequently after the diagnostic instillation of iodized oil to justify its therapeutic use in my clinic, and I believe there is a definite risk of the lung's being harmed by the locking in the alveoli of parts of repeated injections of the oil.

Only in exceptional cases has chemotherapy proved useful. Intravenous arsenicals, which are especially dangerous in patients having a prolonged suppurative disease, have occasionally reduced pulmonary infection when it is caused chiefly by the Vincent's group of organisms. The sulfonamides, whether given by mouth or by nebulizer, have been disappointing in chronic bronchiectasis although, in a few patients, an excellent effect has been produced.

Treatment of infection in the nasal sinuses, nose, mouth and pharynx should be used and may improve the bronchiectasis symptoms. I do not recall a single case, however, in which so-called radical sinus surgery, carried out in the presence of troublesome bronchiectasis, has either completely cured the sinus disease or importantly improved the bronchiectasis symptoms. In my experience radical sinus surgery is much more likely to be effective if deferred until several months have passed after the bronchiectasis has been cured by lobectomy or improved by other treatment. In a few cases, the sinus symptoms will have improved so much that radical surgery is not required.

General hygienic measures are indicated in most cases of bronchiectasis. Ideally, patients who have even mild fever and who are fatigued and underweight should be put to bed for a period of weeks or months under the sanatorium type of regimen or should at least spend long hours in bed at night and two hours in bed after lunch. I am familiar with the work of a pediatrician who has brought about almost miraculous improvement in several children I have seen merely by enforcing regular habits of life, regular postural drainages and, particularly, by expert feeding. Generalized heliotherapy may be helpful as a hygienic measure, but should not be used in febrile patients or in those subject to recurrent attacks of pneumonitis. Anemia should, of course, be treated, by blood transfusions if necessary. Patients who live where the winters are cold and stormy may be benefited by spending the winters in a sunny dry climate which, in some patients, prevents the occurrence of repeated colds and which may also reduce the severity of the nasal sinus symptoms, and the amount of cough and sputum from the bronchiectasis.

Although Watson and Kibler believe that allergic desensitization is highly effective in the treatment of bronchiectasis, I share the experience

of many clinicians in finding it disappointing. The only cases in which I have seen good results from any form of desensitization (including the use of autogenous or mixed stock vaccines for bacterial desensitization) are a few having characteristic symptoms of bronchiectasis but not having any bronchiectases, the symptoms being due to a true allergic bronchitis. In such cases, bronchograms show that the bronchi are abnormally narrow and bronchoscopy reveals swollen pale mucous membrane and mucopurulent secretions.

In certain cases of bronchiectasis with repeated severe hemoptysis, temporary phrenic paralysis may stop the bleeding, but this operation should not be used if the patient has difficulty in raising his bronchopulmonary secretions. In rare instances, retention of secretions in a large bronchiectatic abscess, or in a parenchymal abscess associated with bronchiectasis, may call for surgical drainage of the abscess.

I shall not discuss in this article those forms of therapy that I believe should not be used, namely, induced pneumothorax, roentgen-ray therapy, "the thirst cure," and those many operations that have been proposed, or used with poor results, before the operation of lobectomy was developed to its present status of safety and effectiveness.

### SUMMARY

The many causes of confusion concerning the nature of bronchiectasis, the variability of its clinical behavior, the diagnosis and treatment are discussed. The most frequent sources of error in the management of the disease are considered in detail.

The present safety of pulmonary lobectomy has solved the problem of treatment for approximately half the bronchiectasis patients, but the other half are, for various reasons (especially because of extensive bilateral lesions) not suitable for the operation. Nonsurgical methods of treatment, if properly and faithfully carried out, can be made effective in greatly alleviating the distressing symptoms of the disease in a large majority of patients, in spite of the pessimistic opinions about the value of nonsurgical treatment that have recently been expressed by a number of physicians.

### BIBLIOGRAPHY

1. ADAMS, R., and DAVENPORT, L. F.: The technic of bronchography and a system of bronchial nomenclature, *Jr. Am. Med. Assoc.*, 1942, cxvlii, 111.
2. ALEXANDER, J., and O'ROURKE, P. V.: Evaluation of pulmonary lobectomy, *Univ. [Mich.] Hosp. Bull.*, 1944, x, 9.
3. ANDERSEN, D. H.: Cystic fibrosis of the pancreas, vitamin A deficiency and bronchiectasis, *Jr. Pediat.*, 1939, xv, 763.
4. ANDRUS, P. M.: Chronic nonspecific pulmonary disease, *Am. Rev. Tuberc.*, 1940, xli, 87.
5. ANSPACH, W. E.: Bronchiectasis, collapsed lung and the triangular basal shadow in the roentgenogram and their interrelationship, *Am. Jr. Roentgenol.*, 1939, xli, 173.
6. BOYD, G. L.: Lobar collapse in children, *Jr. Am. Med. Assoc.*, 1935, cv, 1832.

7. BRADSHAW, H. H., CHODOFF, R. J., and DEARDORFF, F. W.: Bronchiectasis, Pennsylvania Med. Jr., 1939, xliii, 29.
8. BRADSHAW, H. H., PUTNEY, F. J., and CLERF, L. H.: The fate of patients with untreated bronchiectasis, Jr. Am. Med. Assoc., 1941, cxvi, 2561.
9. CHAPMAN, J., and ANDERSON, H. M.: Bronchiectasis in general practice and the specialties, Southwest. Med., 1938, xxii, 474.
10. CHURCHILL, E. D.: Bronchiectasis. Physical and psychological manifestations, New England Jr. Med., 1938, ccxviii, 97.
11. CHURCHILL, E. D., and BELSEY, R.: Segmental pneumonectomy in bronchiectasis. The lingula segment of the left upper lobe, Ann. Surg., 1939, cix, 481.
12. CLERF, L. H.: Bronchiectasis: A consideration of its causes and its prevention, Virginia Med. Monthly, 1939, lxvi, 332.
13. DIAMOND, S., and VAN LOON, E. L.: Bronchiectasis in childhood, Jr. Am. Med. Assoc., 1942, cxviii, 771.
14. DOLLEY, F. S., and JONES, J. C.: Lobectomy and pneumonectomy for lung suppuration and malignancy, Jr. Lancet, 1939, n.s. lix, 162.
15. EDWARDS, A. T.: Modern principles of treatment in bronchiectasis, based upon 199 cases treated by lobectomy or pneumonectomy, Brit. Med. Jr., 1939, i, 809.
16. FINDLAY, L., and GRAHAM, S.: Prognosis in bronchiectasis, Arch. Dis. Child., 1931, vi, 1.
17. FLEISCHNER, F.: Pathogenesis of bronchiectasis, Am. Rev. Tuberc., 1940, xlii, 297.
18. FLEISCHNER, F.: Reversible bronchiectasis, Am. Jr. Roentgenol., 1941, xlvi, 166.
19. GALARCE, J. A., and PALADINO, J.: Contribucion al tratamiento actual de las bronquiectasias, Rev. Asoc. méd. argent., 1939, liii, 982.
20. HUGHES, J. G., and SIMPSON, W. L.: Bronchiectasis following atelectasis in tuberculosis in infancy, Jr. Pediat., 1940, xvii, 197.
21. HUIZINGA, E.: Über die Entstehung der Bronchiectasie, Acta radiol., 1940, xxi, 75.
22. LILIENTHAL, H.: The treatment of nontuberculous suppurations of the lung, 9th Congr. Internat. Soc. Surg., Brussels, 1932, ii, 7.
23. LISA, J. R., and ROSENBLATT, M. B.: Bronchiectasis. Pathogenesis, pathology and treatment, 1943, Oxford Univ. Press, London, New York and Toronto.
24. MARQUÉZY, A., LAUNAY, C., LEMOINE, J., and MAGE, E.: L'exploration lipiodolée des bronches au cours de la coqueluche avec expectoration purulente, Bull. et mém. Soc. méd. d. hôp. de Paris, 1939, lv, 158.
25. PASTOR, J. R., and BECERRA, J. L.: Bronquiectasia, Bol. Asoc. méd. de Puerto Rico, 1941, xxxiii, 181.
26. PERRY, K. M. A., and KING, D. S.: Bronchiectasis. A study of prognosis based on a follow-up of 400 patients, Am. Rev. Tuberc., 1940, xli, 531.
27. RIGGINS, H. McL.: Bronchiectasis. Morbidity and mortality of medically treated patients, Am. Jr. Surg., 1941, liv, 50.
28. RILANCE, A. B., and HOWLETT, K. S., JR.: Nontuberculous upper lobe bronchiectasis. A report of three cases, Am. Rev. Tuberc., 1939, xl, 204.
29. ROLES, F. C., and TODD, G. S.: Bronchiectasis. Diagnosis and prognosis in relation to treatment, Brit. Med. Jr., 1933, ii, 639.
30. SHENSTONE, N. S.: Treatment of bronchiectasis, in Frank Howard Lahey Birthday Volume, 1940, Charles C Thomas, Springfield, Ill. and Baltimore, pp. 413-418.
31. SINGER, J. J.: Bronchiectasis, in Modern Medical Therapy in General Practice, 1940, Williams and Wilkins, Baltimore, pp. 2462-2472.
32. Symposium on bronchiectasis by HOLINGER, P. H., RIGGINS, H. McL., ANSPACH, W. E., BRENNEMANN, J., LEDERER, F. L., CLERF, L. H., and DEBAKEY, M. and OCHSNER, A., Dis. of the Chest, 1943, ix, 1.
33. TANNENBERG, J., and PINNER, M.: Atelectasis and bronchiectasis. An experimental study concerning their relationship, Jr. Thoracic Surg., 1942, xi, 571.
34. WATSON, S. H., and KIBLER, C. S.: Bronchiectasis. A new conception of its etiology which makes prevention and recovery possible, Jr. Am. Med. Assoc., 1938, cxi, 394.

## STERNAL PUNCTURE AS A PRACTICAL DIAGNOSTIC PROCEDURE \*

By SIMON PROPP, Lieutenant, M.C., U.S.N.R., and JOSEPH L. SCHWIND,  
PH.D., *Albany, New York*

SINCE the introduction of the procedure by Arinkin<sup>1</sup> in 1927, sternal puncture has been very widely used. Notable contributions to the scientific knowledge of the cytology of bone marrow obtained in this way from patients with various diseases have been made by Arinkin,<sup>2</sup> Nordenson,<sup>3</sup> Segerdahl,<sup>4</sup> Young and Osgood,<sup>5</sup> Vogel, Erf and Rosenthal,<sup>6</sup> Jones,<sup>7</sup> Scott,<sup>8</sup> and others. Most of the punctures reported in the literature have been made for the scientific study of diseases of the hematopoietic system. There are many reports of cases in which the diagnosis was arrived at solely by means of the sternal puncture, but no mention is made of how frequently one may expect to diagnose a given case in this way. Indications for the use of sternal puncture as a diagnostic method have not been clearly established, and the interpretation of marrow findings has not been sufficiently simplified to be of practical value to the average physician.

Recently attempts at evaluation of the procedure have been made by three groups of workers. Kandel and Leroy<sup>9</sup> found sternal puncture to be of relatively little value in the diagnosis of their cases and are of the opinion that "thorough clinical investigation deprives the biopsy of sternal marrow of many of its uses." Falconer and Leonard<sup>10</sup> say: "It is interesting to note that the diagnosis arrived at after thorough study of each case before sternal marrow aspiration was rarely changed by the data subsequently obtained through the study of the marrow cells." No one will argue against the advisability of carrying out a thorough clinical investigation before doing a sternal puncture, unless possibly time is an important factor. However, in many cases exhaustive study ends in no diagnosis or in a questionable opinion and it involves time, expense, and an extended period of worry for the patient and his family. Mendell, Meranze and Meranze,<sup>11</sup> however, say that sternal marrow aspiration "is indicated in all cases suggesting disorders of the blood-forming organs or reticulo-endothelial system." This seems to us to be overly enthusiastic as most cases can be diagnosed without recourse to sternal puncture.

\* Received for publication October 4, 1943.

From the Departments of Medicine and Anatomy, Albany Medical College, Union University, Albany, New York.

The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

We wish to acknowledge our great indebtedness to Dr. L. W. Gorham, Professor of Medicine, for his constant interest, stimulation and assistance, without which this study would have been much more difficult if not altogether impossible.

At the present time, therefore, it is desirable to know whether sternal puncture is an additional diagnostic procedure of reliability, when it should be undertaken, and what practical benefits may be expected from it. The purpose of this paper is (1) to give in detail certain points of practical value in technic and interpretation, (2) to suggest a simple method of reporting the marrow findings so that an understanding of the state of the marrow can be more easily obtained by the average physician, (3) to present the clinical value of sternal puncture under actual working conditions, and (4) to establish indications for its use.

### TECHNIC

All authors have agreed that sternal puncture is a very simple matter. A successful puncture, however, requires a number of rapidly executed technical procedures, and the failure of any one of them may result in an unsatisfactory sample. Unless a novice at the method is forewarned, it is almost certain that his first attempts will yield unsatisfactory results. Some authors advocate very complicated methods of handling the sample of marrow after it is withdrawn. These seem to us quite unnecessary for practical purposes. We have given our technic in detail in the hope that time and effort will be saved for beginners, and that assistance will be given those who have already been disappointed in their efforts to use this procedure.

The technic used in our punctures is very similar to that originally described by Arinkin.<sup>2</sup> The needles are 18-gauge spinal puncture type with a heavy finger grip and a stylet (figure 1). They are cut so that the needle portions are 2, 1.5, and 1 cm. in length. The two longer needles are used for adults, the choice depending upon the build of the individual, and the smallest one is used for infants and children. The shortness of the needles precludes the possibility of accidental perforation into the anterior mediastinum and prevents bending of the shaft of the needle during its insertion. The puncture is made in the midline of the body of the sternum at the level of the third costosternal articulation. This site is easily found, even in obese patients, by using the sternal angle, which marks the second rib, as a reference point. Whenever possible, the lateral margins of the sternum are grasped between the first and second digits of the hand not performing the puncture so that the midline of the sternum may be selected accurately. Proceeding too far laterally may result in failure to enter the marrow cavity. Other levels\* may be used at the discretion of the operator if this site is not available or if a check is desired. In children it is advisable to do the puncture in the third interspace because in some individuals the first and second sternabrae do not unite until adult life is reached. Strict surgical asepsis must be maintained. The skin, subcutaneous tissue and periosteum are infiltrated with novocaine. Some pain is commonly caused when the hypodermic needle penetrates the periosteum to produce local anesthesia. The

\*In six cases in our series similar marrow pictures were found when multiple punctures were done at various levels in the same patient.

periosteum causes a firmer feeling of resistance to the needle than the subcutaneous tissue, and an appreciable sensation of thickness. Upon piercing it, the needle tip strikes the bony anterior plate of the sternum. The final injection of novocaine is then made. A very small amount is sufficient. A total of three cubic centimeters will usually accomplish all necessary anesthesia of the skin and underlying structures. When properly carried out, sternal puncture is not a very painful procedure. Frequently it appears to

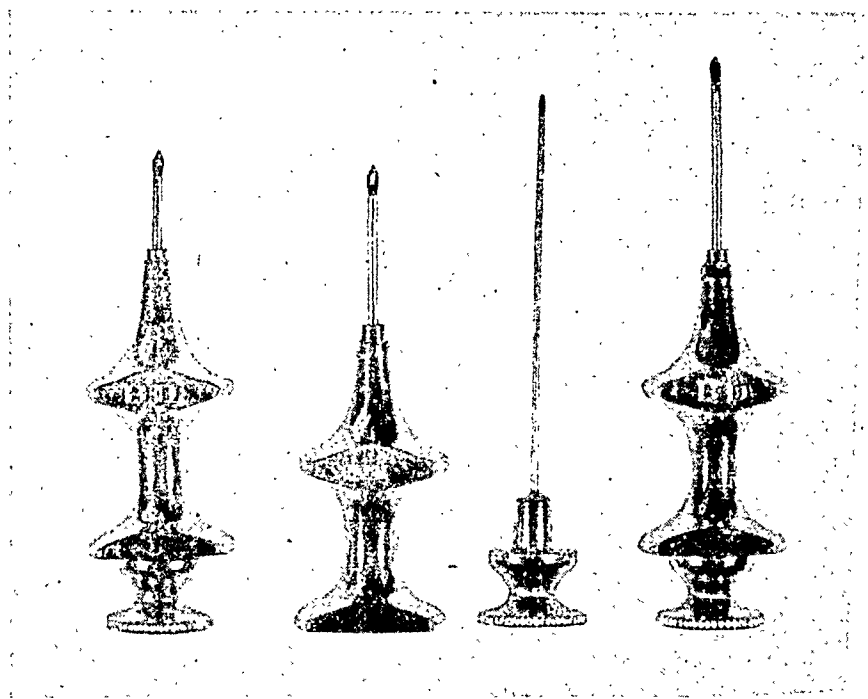


FIG. 1. Full sized photograph of the needles used in doing sternal punctures. The stylet has been removed from the center needle.

produce no appreciable discomfort. The puncture needle is inserted vertically, and the outer table of the sternum is pierced by a rotary movement of the needle under firm pressure. The stylet must be held down firmly so that no bone spicules can enter the tip of the needle to block it during penetration of the outer table. Boring is continued until the needle is firmly fixed in the bone. No dependence is placed on sound or feel when the bone is pierced, as in many punctures there is no indication that the medullary cavity has been reached, i.e., the so-called "give" may be absent. When the needle is firmly fixed in the sternum, the stylet is removed, a tuberculin syringe is attached to the needle, and aspiration is attempted. If no marrow fluid appears, the stylet is replaced, the needle is advanced a little farther, and aspiration is again tried. This is continued until marrow fluid, which has the gross appearance of ordinary blood, appears in the syringe. This may be preceded and accompanied by a painful sensation in the chest, evidently the result of producing a negative pressure in the marrow cavity. The pain is never

severe in character. Occasionally, no material is obtained with the tuberculin syringe, and it is necessary to use a larger syringe (5 to 10 c.c.) to produce a greater suction, in order to be sure that no cells can be detached from inside the marrow cavity. This is more likely to occur in cases in which there is a replacement of bone marrow by pathological tissue as in Hodgkin's disease, reticulosis, and other similar diseases.

One-tenth to 0.2 c.c. of marrow fluid is withdrawn. This quantity has given the best results in our punctures. Aspiration of more fluid serves no purpose and in some instances greatly dilutes the marrow sample with peripheral blood. Taking a smaller amount sometimes results in failure to aspirate a sufficient amount of marrow for study. There is always an admixture of sinusoidal blood in the sample, the amount probably varying from puncture to puncture, as well as with the volume of fluid removed. Therefore, total counts of cells in the puncture fluid have not been done in our study.

Care must be taken to stop suction before the needle and its attached syringe are withdrawn, together, from the sternum. It is essential that the marrow sample remain in the puncture needle and the lower part of the syringe. It is necessary therefore, to hold the plunger firmly in place, during withdrawal or the marrow fluid may be sucked up into the syringe when the needle comes out of the bone, or the weight of the plunger may force the fluid out of the needle before the operator is ready for it. As soon as the needle is withdrawn from the sternum (with the tuberculin syringe attached) it must be quickly turned to a horizontal position to prevent the extrusion of drops of marrow fluid at the free end. A sterile compress is then applied to the puncture wound and held in place by adhesive for 48 hours.

The most satisfactory portion of the specimen for study is that which enters the needle last and, therefore, is used in making the first smears. The portion which enters the needle first, in our experience, may contain only sinusoidal blood. It is necessary to work rapidly in making the smears as clotting occurs quickly in the needle. Coating the needle and syringe with sterile vaseline allows a more leisurely procedure, but it has not been found to be really necessary. Anticoagulants such as sodium citrate or potassium oxalate sometimes interfere with the staining of the marrow cells.

To make the smears, the tuberculin syringe and its attached puncture needle are held horizontally, with the opening of the needle facing downwards, and small drops of marrow fluid are made to appear at the opening by gently pushing in the plunger. Great care must be used in doing this or the drops expressed from the needle will become too large. A number of dried smears, at least 12, are made directly on scrupulously clean covers slips only. The drops of marrow fluid placed on the slips for smearing must be very small. The cells on the smears should lie close together but not overlap. If the films are too thick they do not stain well. If they are too thin, many of the more fragile cells will break up. The smear must be dried quickly



or it will not stain properly. All smears of marrow in which fat cells are present in the marrow cavity contain fat droplets. This fact may be used as an indication that the aspirated material actually came from the marrow cavity, a point which is sometimes doubtful in extremely hypoplastic marrows. The smears are stained with Wright's stain, which we have found to be quite satisfactory. The stain is carefully made up and is used without dilution. Wright's stain is easier to use than May-Gruenwald-Giemsa, and moreover all physicians are familiar with the appearance of cells stained by this method. The importance of good smears and proper staining cannot be overemphasized.

To make reticulocyte counts, scrupulously clean slides are prepared by flooding them with a saturated solution of brilliant cresyl blue in 95 per cent alcohol, draining off the excess and allowing them to dry in a vertical position. If small particles of dye appear on the slide, the marrow film will not spread evenly. Such particles can be removed by gently polishing the dried cresyl blue on the slide with lens paper. A small drop of marrow fluid is placed on a cover slip which is then inverted upon the cresyl blue slide. The edges of the coverslip are rimmed with vaseline to prevent evaporation and subsequent crenation of the erythrocytes.\* The count must be made within one hour after preparing the film if the slide is left at room temperature. For the sake of uniform procedure, the second drop which comes out of the needle is used to make the reticulocyte preparation. The nuclei of all the cells stain heavily and this slide is also used for estimating the degree of cellularity of the marrow. Naturally, the cellularity may be also estimated from the dried smears.

Supravital preparations are also made of every puncture for comparison with the dried films. These are not an essential part of the procedure, but may be of help in the identification of monocytes.†

### MATERIAL

Our material consists of 140 cases of diseases of the blood and hematopoietic system and cases in which the possibility of such disorders entered into the differential diagnosis. Twenty punctures on patients ranging in age from 17 to 41 years without hematological disorders served as normal standards. Our differential counts on this latter material are in agreement with the results obtained by other authors for normal marrow.

\* It is generally agreed that "wet" methods of counting reticulocytes are preferable to "dry" methods, as the latter do not always stain all the reticulocytes. The statement of Mendell, Meranze and Meranze that "reticulocytes in the bone marrow in relapse (of pernicious anemia) were too few to be counted" is not supported by this study. In our series the lowest reticulocyte count in the marrow in this condition was 0.4 per cent, and the most severely anemic case we have seen had 3.1 per cent.

† Vogel, Erf and Rosenthal found monocytes present in only two of 246 punctures. Monocytes can be identified in almost all punctures when studied with the supravital method, though it must be admitted that we have not been able to find them as frequently in the dried smears.

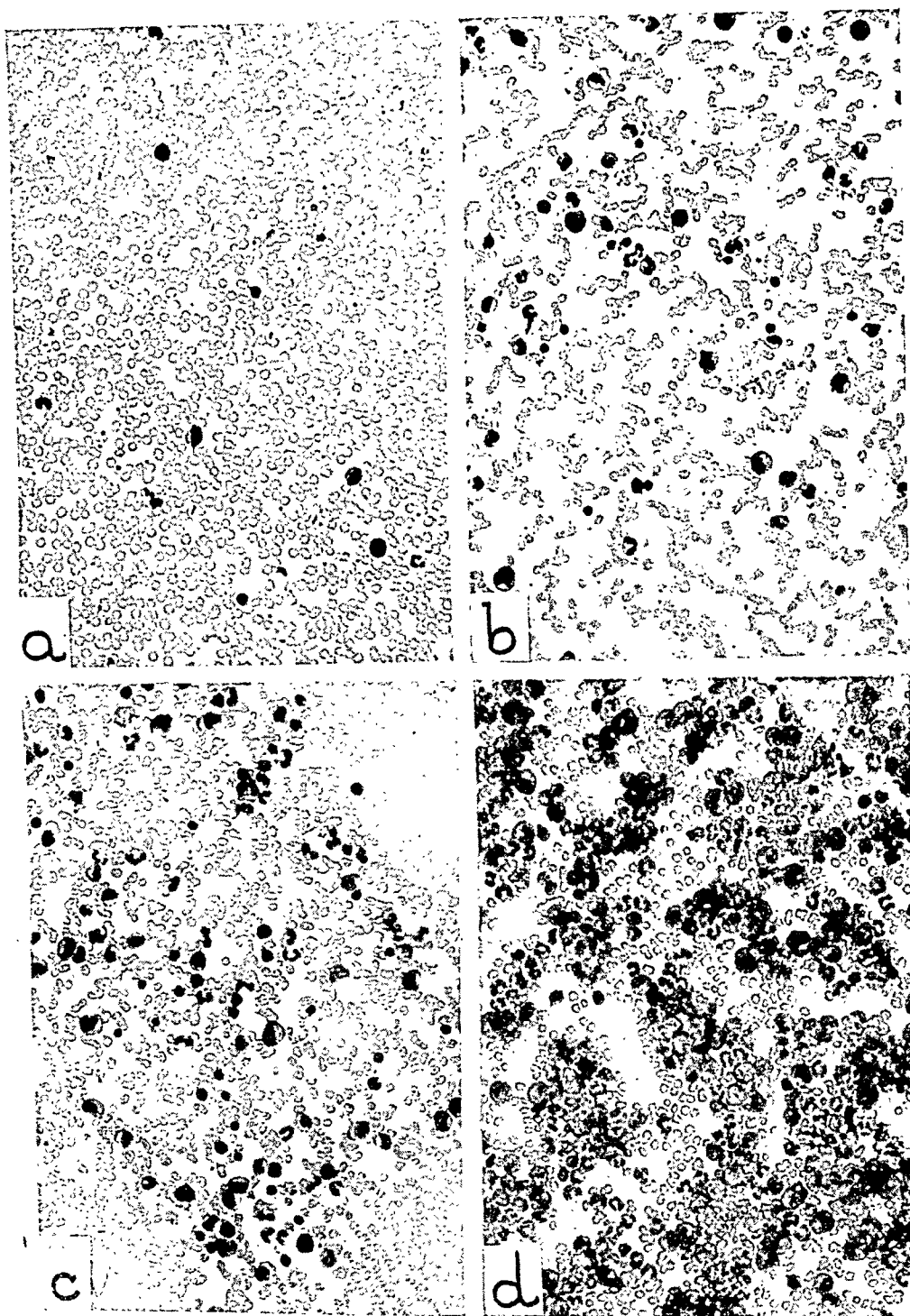


FIG. 2. Grades of cellularity found in smears of marrow aspirated from sternal punctures. *a*, Grade 1, from a normal individual; *b*, Grade 2, from a normal individual; *c*, Grade 3, from a normal individual; *d*, Grade 4, from a case of chronic myelogenous leukemia. The photographs show the dispersion of nucleated cells when viewed with the 16 mm. lens.  $\times 170$ .

## CYTOLOGY

A working knowledge of the cells in normal marrow is, needless to say, indispensable for the proper interpretation of the marrow picture in disease. The marrow fluid obtained by sternal puncture in normal individuals is, in our experience, extremely variable in its cellularity. For purposes of record, we have arbitrarily graded the cellularity of the marrows in our series into four groups or grades (figure 2). Grade 1 marrows have approximately the number of nucleated cells found in peripheral blood smears. Grade 2 marrows have four to five times this number of cells, whereas Grade 3 marrows have from 10 to 12 times that number. In Grade 4 marrows there are more nucleated cells than erythrocytes, and the cells appear on the smears in clumps and masses. Such a grouping is, of course, grossly inaccurate, but repetition of the puncture in 16 cases showed that the individual had the same grade of cellularity in the second puncture as he had in the first. It may be assumed, therefore, that with a standardized technic, such a grading of the cellularity of the marrow samples gives at least a rough idea of the degree of hypoplasia or hyperplasia present in the marrow cavity. Grades 1, 2, and 3 all occur in normal individuals, as well as in a variety of diseases, though Grade 2 is the most common normally. Grade 4 marrows occur only in individuals in whom the bone marrow is extremely hyperplastic, such as chronic leukemias and some cases of pernicious anemia and hemolytic anemia.

The predominant cells in normal marrow belong to the neutrophilic series of granulocytes. In Grade 1 normal marrows, the one numerically predominant cell is a neutrophile with a segmented nucleus, whereas in Grade 3 normal marrows the predominant cell is a neutrophile with a band form (single lobed) nucleus. In Grade 2 normal marrows these two types of cells occur in almost equal numbers so that in some marrows the segmented neutrophiles predominate and in others the band forms are the most numerous. How much of the variation in cellularity and predominant cell type is due to dilution of the marrow sample with peripheral blood is at present unknown. The older cells of the series are more numerous, but all the younger cell types down to and including the myeloblast are always present. The terminology applied to the granulocytic cells of the marrow in this paper is as follows: (1) Cells which contain only specific (in this instance neutrophilic) granules and are distinguished by their nuclei include the segmented forms with two or more lobes in the nucleus; the band forms in which the nucleus has only one lobe; metamyelocytes, which have bean shaped nuclei; and myelocytes, in which the nucleus is round or oval. (2) Cells which contain both specific (neutrophilic) and azure granules are termed the promyelocytes. (3) Cells which contain only azure granules or are completely agranular are called leukoblasts and myeloblasts. Leukoblasts contain azure granules, may or may not have nucleoli, and have a definite nuclear membrane. Myeloblasts contain nucleoli, may or may not have azure granules in the cytoplasm, and the nuclear membrane is indistinct. Not all investigators recognize a leuko-

blast stage; such cells are probably classified by them partly as promyelocytes and partly as myeloblasts. Though of great theoretical interest, this question has at the present time no practical importance in diagnosis. In our material, the actual percentages of neutrophilic cell types based on differential counts of 500 cells from smears stained with Wright's stain on 20 normal marrows are as follows: \* segmented neutrophils 7.4–25.0 per cent, band forms 17.6–46.4 per cent, metamyelocytes 5.6–14.2 per cent, myelocytes 3.2–10.6 per cent, promyelocytes 2.2–8.0 per cent, leukoblasts, 0.4–3.0 per cent, myeloblasts 0.4–2.0 per cent.

Eosinophilic cells are also present in small numbers, 0.6 per cent–5.5 per cent. Most of these cells are the more mature forms, segmented and band forms, eosinophiles. Eosinophilic promyelocytes are rarely seen in normal marrow. Even smaller numbers of basophilic cells are normally found—from none at all to 0.8 per cent, almost all of them mature.

The cytology of the development of the red cells has been very thoroughly studied by Jones,<sup>7</sup> from whose article the substance of this section has been taken. In normal marrow, the erythroid cells are all of the normoblastic line. The earliest recognizable cell of this line is the pronormoblast, which is somewhat similar to the myeloblast in appearance. It is a large cell with a large nucleus, which may contain distinct nucleoli. It differs from the myeloblast in having a more condensed and homogeneous and more basophilic cytoplasm which contains no azure granules. The strands of chromatin in the nucleus are thicker than in the myeloblast, and there is not as much parachromatin. The next stage in the development of normal red cells is the basophilic normoblast, which has no nucleoli and does not in any way resemble the myeloblast. The cytoplasm is even more basophilic than in the pronormoblast, though it is sometimes not as homogeneous and condensed. As the pronormoblast matures, the individual granules of chromatin begin to fuse together or clump, and notches and crevices appear in the parachromatin, so that in the basophilic normoblast the chromatin has the appearance of coarse granular filaments. In late stages, some of these cells may show a wheel spoke (Radkern) arrangement of chromatin in the nucleus. The nucleus is smaller in proportion to the amount of cytoplasm than in the preceding stage. Hemoglobin is then developed in the cytoplasm, so that the intense basophilia is lost, making the polychromatic normoblast, and when the full complement of hemoglobin is present, the cell is called the orthochromatic normoblast. The nucleus becomes progressively more pyknotic during these changes and is finally dissolved, broken up or extruded from the cell, making the normal-sized erythrocyte. The actual percentages of erythroid cell types in our normal marrows are as follows: pronormoblasts 0.4–1.4 per cent, basophilic normoblasts 0.6–3.2 per cent, polychromatic normoblasts 2.6–17.6 per cent, orthochromatic normoblasts 0.4–4.8 per cent.

\* All data on differential counts given in this section are 90 per cent central normal ranges, determined by Thompson's<sup>12</sup> method.

Marked hyperplasia of the normoblastic cell line, with an increase in the percentage of all its cell types, occurred in our series of cases in iron deficiency, acute hemolytic and sickle cell anemias, in the anemia due to acute hemorrhage, congenital hemolytic jaundice, and in secondary polycythemia. A lesser degree of hyperplasia was found in many other conditions.

A second type of erythroid cell which is never found in normal marrow is, however, present in some hematological disorders such as pernicious anemia in relapse; achrestic anemia and sprue, and occasionally in leukemia, hemolytic anemia, "aplastic" anemia and certain other diseases.<sup>13</sup> These cells give rise to the large-sized red cells (megalocytes) which are characteristic of the macrocytic hyperchromic anemias, and are known as the megaloblastic line of cells.

Many hematologists are apparently not aware of the existence of this second type of developing red cell \* probably because they rarely occur in the peripheral blood and at the present time cannot be produced readily by experimental procedures. They are easily recognized in stained smears of the bone marrow in the above-mentioned diseases, but are less evident in supravital preparations.<sup>14</sup>

A complete series of developmental stages can be made out for them corresponding to similar stages in the normoblastic line. The earliest stage, the promegaloblast, is a large cell with a nucleus which is coarser than that of the myeloblast, and the cytoplasm is more basophilic. The cytoplasm is not, however, as dense and homogeneous as in the pronormoblast, and contains perinuclear light areas which give it a mottled appearance. The nucleus is smaller, compared to the size of the cell, than in the pronormoblast. The nucleoli are fainter in outline, and more or less masked by the chromatin reticulum. There is more parachromatin than in the pronormoblast, and less tendency for the chromatin to clump as the cells mature. The uniform distribution of chromatin throughout the nucleus and the absence of clumping of the chromatin threads until the very latest stage of development is reached is characteristic of this line of cells. The basophilic megaloblast is a smaller cell, but it is larger than the corresponding basophilic normoblast, and its cytoplasm is more basophilic and more homogeneous than that of the promegaloblast. There are no nucleoli. The chromatin reticulum is composed of small masses which are separated from one another by curved areas of parachromatin. In later stages, these curved areas become rounded, so that the

\* There is at present considerable confusion in the terminology of the erythroid cells. The term megaloblast is used (1) as in this paper, to mean a dysplastic cell in which the nuclear chromatin forms a looser framework and has less tendency to form clumps and dense masses than does the nucleus of an erythroid cell of corresponding stage of development in normal marrow, and which is occasionally found in the peripheral blood but typically in the marrow in cases of pernicious anemia and sprue, (2) as the name of the earliest recognizable erythroid cell found in the marrow. The details of this controversy are beyond the scope of the present paper, but it is a matter of practical importance for if the second view were correct the marrow of pernicious anemia in relapse could not be distinguished from that of hemolytic anemia or from post-hemorrhagic marrow. For an exhaustive discussion of this problem, the reader is referred to Jones' <sup>15</sup> recent article.

nucleus looks rather like a sieve. The chromatin never forms a wheel type of nucleus. The sieve-like appearance of the nucleus persists through the polychromatic megaloblast stage, and only in the orthochromatic megaloblast, when the degeneration of the nucleus begins, is there any formation of large clumps and masses of chromatin. At a corresponding stage, the orthochromatic normoblast has a completely pycnotic nucleus. The cytoplasm of the megaloblastic cells remains disproportionately large compared to the size of the nucleus, and the disproportion grows more pronounced as the cell matures. Many large orthochromatic megaloblasts are found with small nuclei which are still vesicular and immature in appearance. Most megaloblastic cells are considerably larger than their homologues in the normoblastic line. However, after the nucleus has become completely pycnotic, it is sometimes difficult to distinguish small orthochromatic megaloblasts from large orthochromatic normoblasts. It should be borne in mind that all diseases in which megaloblasts are present also have normoblasts in the marrow to a varying extent.

In most of our normal subjects the reticulocyte count in the marrow was 0.5–2 per cent, but in one apparently normal individual, it was 3.7 per cent. We have, therefore, adopted 4 per cent as the upper limit of normal in order to be on the safe side, although this figure is probably somewhat too high.

Small numbers of lymphocytes, mostly of the small type, monocytes and plasma cells, all of mature form, are found in all normal smears. Immature forms of these cells are not normally encountered. At present, it is not known how many of the first two groups are actually in the marrow and how many are due to admixture of sinusoidal blood with the sample. Marrows from individuals having a lymphocytosis in the peripheral blood will naturally show an increased number of lymphocytes in the marrow smears. It must also be remembered that there are said to be occasional small lymph nodules in the marrow, and therefore an increase of lymphocytes is not necessarily of importance.

Megakaryocytes are easily recognized even with the low power objective. They are never numerous, and many of them are probably broken up in making the smears.

Cells in mitosis are found in all normal marrows, but they too are not numerous.

Reticulum cells and macrophages are occasionally found. "Ferrata" cells are in our opinion merely damaged cells, as has been suggested by Ringoen, but we doubt if they are produced solely from promyelocytes. They are absent from most smears, but sometimes occur in smears of abnormal marrows. We have not been able to find any small cells, either in the dry smears or in the supravital preparations which answer to the descriptions of "hematogones" as given in some of the literature. These cells are most probably overstained small lymphocytes.

The ratio of the number of all types of white blood cells and their pre-

cursors to the number of all types of nucleated red cells present in the sample we have called the myeloid-erythroid ratio. This ratio varies from 3:1 to 50:1 in normal individuals, and varies in the same individual on successive punctures. The variation is most probably due to the relatively small number of cells which are examined in a differential count as well as the error introduced by the unavoidable dilution of the marrow with sinusoidal peripheral blood. We have not found this ratio to be of much practical significance, although it is a convenient way of comparing the two groups of cells. Occasionally in anemias, this ratio approaches unity or is actually reversed, whereas in chronic leukemia the white cells greatly outnumber the erythroid series.

A certain number of cells in every puncture, from normal as well as abnormal marrow, cannot be identified, due to unavoidable injury to the cells in making the smears and to defects in the drying and staining process caused by fat droplets and the piling up of the nucleated cells. In normal marrow this number varies from 0.2 to 2.0 per cent, when the best parts of the smear are selected for study. Some abnormal marrows have many more cells which cannot be identified, the number depending partly on the skill, training, and optical equipment of the observer, but with a reasonably well-trained individual they are of no practical significance.

#### CLINICAL MATERIAL

A listing of all the diseases studied is given in table 1. After a careful review of these cases, they have been divided into three categories: (1) 74 cases in which sternal marrow punctures were actually indicated clinically; (2) 22 cases in which sternal punctures were done at the request of the attending physicians, but which by the criteria developed during this study were not indicated; (3) 44 cases in which punctures had been done to obtain specific information concerning the character of the marrow for research purposes, but which were not necessary for diagnosis.

The diseases included in the group of the 74 indicated cases are shown in table 2, and the value of these punctures is given in table 3. It can be seen that almost 65 per cent of the punctures for which there was an actual indication were of use clinically, and indeed the diagnosis was made by means of the puncture in 16.2 per cent of the cases where all other diagnostic means short of surgical biopsy had failed. In 35.1 per cent of the indicated punctures no results of clinical value were obtained, but nine of these 26 cases were of value for research purposes. Seventeen cases resulted in findings which were of no practical use either clinically or scientifically, and have been listed as being of "no value."

The results of the 22 punctures which were performed on request, though not actually indicated, are in marked contrast to the above findings: no information of clinical value was obtained from any of them. The correct diagnosis was made in one of these cases (4.5 per cent) by means of the

puncture, but this was of no practical help as it only established the correct type of an already diagnosed acute leukemia. Six of these punctures were of value for research work (27.3 per cent), but 15 of the 22 cases (68.2 per cent) were of no value at all. The pessimism shown in some of the more recent papers about the value of sternal punctures in diagnosis may be due to equally poor selection of cases for study.

TABLE I

## Final Diagnosis on Cases Punctured

Agranulocytosis.....	5
<i>Anemia</i> .....	38
Achloric.....	1
Aplastic.....	2
Hemolytic.....	4
(Congenital jaundice—1)	
Hypochromic.....	12
Macrocytic.....	2
(Liver disease—1)	
Pernicious.....	16
Sickle cell.....	1
Banti's disease.....	1
Felty's syndrome.....	1
Hodgkin's disease.....	5
Infectious mononucleosis.....	2
<i>Leukemia</i> .....	31
Acute lymphatic.....	2
Acute monocytic.....	1
Acute myelogenous.....	7
Chronic lymphatic.....	7
Chronic myelogenous.....	7
Aleukemic, myelogenous.....	7
Leukemoid reaction.....	2
Lipoid histiocytosis.....	1
Malignant diseases.....	14
Mycosis fungoides.....	2
Myeloma, multiple.....	1
Osteosclerosis.....	1
Periarteritis nodosa.....	1
Polycythemia vera.....	2
Polycythemia, secondary.....	2
Sprue.....	1
Thrombocytopenia, primary.....	2
Thrombocytopenia, secondary.....	2
Wilson's disease.....	2
Miscellaneous.....	13
No diagnosis.....	11
Total.....	140

In the 44 cases which were done for research purposes, the correct type of an acute leukemia was established in one case (2.3 per cent); one case was diagnosed by means of the puncture, but could in our opinion have been diagnosed by other means (2.3 per cent); 34 cases were of research value (77.3 per cent); and eight punctures were of no value (18.1 per cent). No



TABLE II

## Final Diagnosis on Clinically Indicated Punctures

Agranulocytosis.....	5
<i>Anemia</i> .....	10
Achrestic.....	1
Aplastic.....	2
Hemolytic.....	2
Hypochromic.....	1
Pernicious.....	4
Banti's disease.....	1
Felty's syndrome.....	1
Hodgkin's disease.....	4
Infectious mononucleosis.....	2
<i>Leukemia</i> .....	13
Acute lymphatic.....	1
Acute myelogenous.....	2
Chronic lymphatic.....	2
Chronic myelogenous.....	1
Aleukemic myelogenous.....	7
Leukemoid reaction.....	1
Lipoid histiocytosis.....	1
Malignant diseases.....	11
Mycosis fungoides.....	1
Myeloma, multiple.....	1
Osteosclerosis.....	1
Periarteritis nodosa.....	1
Thrombocytopenia, primary.....	2
Thrombocytopenia, secondary.....	1
Miscellaneous.....	8
No diagnosis.....	10
Total.....	74

TABLE III

Punctures Indicated Clinically  
(74 cases)

Results of:	Number of Cases	Percentage of Group
Clinical Value.....	48	64.9
Correct diagnosis made by means of puncture.....	12	16.2
Correct diagnosis made by means of puncture but possible other- wise.....	2	2.7
Confirmatory in doubtful cases.....	4	5.4
Contributory to differential diagnosis.....	26	35.1
More rapid diagnosis.....	2	2.7
Prognostic value.....	2	2.7
No Clinical Value.....	26	35.1
Useful for research.....	9	12.2
No value.....	17	23.0

further reference will be made to the sternal punctures which were not clinically indicated.

No accidents or infections occurred in any of our punctures. There were no failures to obtain a sample except in cases in which it was subsequently proved that the bone marrow was completely aplastic, or in which it had been replaced by some other type of tissue.

The clinical value of sternal marrow punctures can best be shown by brief reference to the case histories.

#### CASE REPORTS

##### *I. Correct diagnosis made by means of puncture.*

*Case 1.* A 78-year-old white man had been ill for two months with the chief complaints of weakness, swelling of the feet and extreme pallor. Slight splenic enlargement was found. The blood showed hemoglobin 6.6 grams, 45 per cent; red blood cells 2,224,000; color index 1.0; white blood cells 4,800; differential count: neutrophiles 68 per cent, small lymphocytes 28 per cent, eosinophiles 4 per cent.\* Macrocytosis, anisocytosis, poikilocytosis and polychromatophilia were present in the red cells. No immature cells were found. Free hydrochloric acid was present in the gastric contents. On two occasions, a trace of blood was found in the feces by the benzidine test. A gastrointestinal series, intravenous pyelogram, barium enema and proctoscopic examination were negative. A later barium enema showed diverticulosis of the colon. He had been treated with very large dosage of parenteral liver extract and ferrous sulphate without improvement. At the time of puncture the latest blood count showed: hemoglobin 7.0 grams, 48 per cent; red blood cells 1,752,000; color index 1.4; white blood cells 4,000; neutrophiles 50 per cent, small lymphocytes 40 per cent, eosinophiles 10 per cent. A diagnosis could not be made. Sternal puncture revealed a hyperplastic marrow with a left shift in the granulocytic series (neutrophilic metamyelocytes predominating) and a marked hyperplasia of the red cell line. Large numbers of pronormoblasts and promegaloblasts were present as well as the later stages of both lines of cells. A diagnosis of achrestic anemia was made from the marrow findings in association with the clinical picture. Following puncture the patient was transfused and great improvement occurred. Gradual decline, necessitating more transfusions, followed.

This puncture enabled the clinician to obtain an insight into the case which otherwise would have remained extremely puzzling. There can be no question here of a case of pernicious anemia treated with an inadequate amount of liver extract, as this patient had received 15 units of liver extract daily for 15 days just before the puncture was performed, and moreover gastric free hydrochloric acid was present.

*Case 2.* A 34-year-old white, married female was admitted to the hospital with a temperature of 103° F. She had been ill with pain in the right hip and sacroiliac region for about five weeks, and had been treated in another hospital with a sulfonamide. She was referred because of persistent granulocytopenia. On admission, there was tenderness in the sacroiliac region bilaterally, in the right hip and later in both shoulder and acromio-clavicular joints. Pelvic examination showed bilaterally adherent and tender adnexa. A vaginal discharge was present in which no gonococci were found. No lymphadenopathy was present and the spleen was not palpable. The blood count on admission was: hemoglobin 9.5 grams, 67 per cent; red blood cells 3,400,000; white blood cells 12,700; neutrophiles 25 per cent, eosinophiles 2 per cent, lymphocytes 72 per cent, monocytes 1 per cent. The clinical diagnosis was pelvic inflammatory disease, gonorrheal arthritis, lymphocytic reaction to sulfonamide medication. Sulfanilamide was given for three days, 15 grains every four hours. On the third day, blood count was: hemoglobin 9 grams, 63 per cent; white blood cells 7,100; neutrophiles 28 per cent, lymphocytes 72 per cent. Blood sulfanilamide 7.8 mg. per cent free, 10.4 mg. per cent total. The fourth day, following a blood transfusion,

\* Some of these cases were seen in consultation and the laboratory work which had been done on them was not as complete and in some instances probably not as accurate as would have been desirable.

blood examination showed: hemoglobin 11.9 grams, 83 per cent; red blood cells 3,380,000; white blood cells 3,200; neutrophils 26 per cent, lymphocytes 69 per cent, eosinophiles 1 per cent, monocytes 4 per cent. Coagulation time was three minutes by capillary tube, bleeding time (Duke), 20 minutes. Just before the sternal puncture was done, with the total counts essentially unchanged, 5 per cent lymphoblasts were noted in the differential: segmented neutrophils 2 per cent, bands 24 per cent, metamyelocytes 8 per cent, myelocytes 2 per cent, eosinophiles 4 per cent, basophiles 1 per cent, monocytes 4 per cent, lymphocytes 50 per cent, lymphoblasts 5 per cent. Blood platelets were greatly reduced. Sternal puncture revealed a marrow of normal degree of cellularity but 91 per cent of the marrow cells were of the lymphocytic series and 46 per cent of these were lymphoblasts. Diagnosis: Acute lymphatic leukemia in sub-leukemic phase. Before death the peripheral blood picture became frankly leukemic. The diagnosis was confirmed at autopsy. Sternal puncture of this case during the first hospitalization would probably have indicated the correct diagnosis.

*Case 3.* A 34-year old white male had been having trouble with aching of his teeth for four months. Three days before admission a swelling developed in the region of the third right lower molar. This ruptured and drained bloody, purulent material. Fever of 101° to 102° F. was present. On admission he showed marked pallor, appeared toxic, and had a necrotic lesion of the right lower jaw. There was slight lymphadenopathy, an enlarged spleen felt three fingers'-breadth below the costal margin, and slight enlargement of the liver.

Blood studies: hemoglobin 7.5 grams, 51 per cent; red blood cells 2,670,000; white blood cells 5,000; segmented neutrophils 17 per cent, bands 18 per cent, metamyelocytes 3 per cent, myelocytes 3 per cent, eosinophiles 1 per cent, basophiles 1 per cent, lymphocytes 34 per cent, unidentified cells 23 per cent. Three per cent of the latter cells contained nucleoli. With Wright's stain, the unidentified cells seemed to belong to the monocytic group of cells, but with supravital staining they resembled lymphocytes. Moreover, peroxidase staining gave 46 per cent positive and 54 per cent negative, so that no definite conclusion could be reached as to the type of aleukemic leukemia which this patient had. Sternal puncture revealed a marrow of a normal degree of cellularity, but the predominating cell was a myeloblast. All later stages in the development of neutrophils, eosinophiles and basophiles were present, but in greatly reduced numbers; the red cell line was hyperplastic (myeloid erythroid ratio 1.5:1) and megaloblasts were present, although the majority of the developing red cells were normoblastic. Diagnosis: acute myelogenous leukemia, leukopenic, confirmed at autopsy.

This puncture, though of no practical benefit to the patient, nevertheless gave the correct diagnosis, which could not be made from the peripheral blood.

*Case 4.* A white male, 70 years of age, had had a resection of his prostate. He continued febrile for eight days, when a scrotal abscess was drained. However, his general condition did not improve and he continued to have fever without obvious cause. During the next eight weeks, his total white blood cell count fell from 21,350 to 5,900 with a marked left shift to 19 per cent myelocytes, and his hemoglobin was 6 grams, 41 per cent and red blood cells 2,140,000. The clinical impression at this time was aleukemic myelogenous leukemia. Sternal puncture showed a hyperplasia of the marrow in the granulocyte series, with a left shift, the dominant cell being a neutrophilic metamyelocyte. Promyelocytes were increased in number, but the percentage of myeloblasts was normal. Red cell formation was below normal. Diagnosis: Leukemoid marrow reaction to infection. *Staphylococcus aureus* was repeatedly isolated from blood culture. He was treated with sulfathiazole and transfusions, and after a month was discharged from the hospital improved. He subsequently developed further localized suppurative infections and granulocytopenia. He recovered and a little over one year later there was no evidence of leukemia.

*Case 5.* A 38-year-old white male was ill for two months, starting with fever, sore throat and enlarged spleen, which was treated with sulfanilamide, at first with marked improvement. Recurrence with sore throat, fever, and splenomegaly followed, and was complicated by jaundice, pneumonia and anemia. Laboratory data: hemoglobin 10.3 grams, 70 per cent; red blood cells 3,700,000; white blood cells 44,000; 94 per cent large primitive appearing cells considered by another (very well known) laboratory to be indicative of acute leukemia; heterophile antibody test negative. Our differential count on the day of the puncture was: segmented neutrophils 17 per cent, bands 12 per cent, eosinophiles 2 per cent, basophiles 1 per cent, monocytes 5 per cent, large lymphocytes 3 per cent, intermediate lymphocytes 32 per cent, small lymphocytes 28 per cent. The sternal puncture showed a marrow with a normal degree of cellularity and a normal distribution of cell types except for a marked lymphocytosis. Both in the marrow smears and in the peripheral blood, many of the lymphocytes showed changes which are typical of infectious mononucleosis. No lymphoblasts were seen in any of the marrow smears. Correlation of the marrow findings with the clinical picture indicated a diagnosis of infectious mononucleosis. Complete recovery ensued.

This diagnosis could have been made by further observation and study without puncture, but was made with confidence immediately following this procedure.

*Case 6.* A white male 44 years of age had been troubled for five months with weakness, general malaise, persistent headaches, and sharp shooting pains in the back and legs. There were periods of remission and exacerbation. His illness had started with chills and fever while working in Panama. This had lasted for four weeks. He had been treated with quinine and neoprontosil. Four blood transfusions had made him feel better temporarily. He had been in two other hospitals for study but was discharged undiagnosed. In this hospital his chief complaints were persistent headaches, weakness and insomnia. Physical examination showed only malnutrition and pallor. Gastrointestinal roentgenographic series and barium enema were negative. Laboratory data: hemoglobin 11.5 grams, 79 per cent; red blood cells 3,260,000; color index 1.2; white blood cells, 8,600; segmented neutrophils 18 per cent, bands 42 per cent, metamyelocytes 4 per cent, myelocytes 4 per cent, promyelocytes 2 per cent, eosinophiles 1 per cent, basophiles 1 per cent, monocytes 11 per cent, lymphocytes 17 per cent; a few normoblasts were seen in the smear; reticulocyte count 2.7 per cent; sedimentation rate 22 mm. in one hour (Walton), very rapid; non-protein nitrogen 26; gastric analysis following histamine, 0.2 per cent free hydrochloric acid; icterus index 3; serum bilirubin less than 0.5 mg. per cent. No clinical diagnosis could be made. Sternal punctures were done opposite the third, fourth, and fifth costosternal articulations in mid-sternum. In all of them the sternum was penetrated with great difficulty to a depth of at least 1 cm. without encountering a marrow cavity. In the first two no fluid could be aspirated at all, even under strong suction (with a 10 c.c. syringe). In the third a few drops of bloody fluid were obtained which contained fat but very few marrow cells. These consisted of myelocytes and normoblasts which were somewhat less mature than those in the peripheral blood. It was, therefore, suspected that this patient had no marrow cavity in the sternum, and a trephine biopsy was done. (It is interesting to note that under novocaine anesthesia this patient experienced sharp pains which were very disturbing in the three punctures and during the trephining, when the needles and trephine were actually through the periosteum and in the bone itself.) Sections of the trephine biopsy showed heavy bony trabeculae where the marrow cavity should have been. The space between the trabeculae was filled in with fibrous tissue and an eosinophilic mass resembling osteoid tissue. Very small islands of marrow and isolated marrow cells were occasionally present. Diagnosis: osteosclerosis with myelophthisic anemia. Radiographs showed that the skull, pelvis, vertebrae, sternum and shafts of the femora were sclerotic. The blood calcium

was found to be 13.7 mg. per cent; blood phosphorus 3.2 mg. per cent; the phosphatase was 24 Bodansky units. Eight days later repetition of the chemical analyses of the blood showed blood calcium, 9.3 mg. per cent; phosphorus, 4.3 mg. per cent; and phosphatase, 51 Bodansky units. This patient died three weeks later in another city and no autopsy was obtained.

*Case 7.* A 61-year-old white male complained of abdominal distress of six months' duration. He had attacks of severe pain in the upper abdomen and beneath the sternum which was cramp like and relieved by belching or passing flatus. The attacks lasted several hours, and although they were infrequent at first were now increasingly troublesome. Two weeks before admission his gait had become unsteady. On admission to the hospital he showed marked pallor, an icteric tinge to the sclerae, a normal tongue, a symmetrically enlarged prostate, hypoactive reflexes, vibration sense was normal and Romberg test negative.

*Laboratory Data:* hemoglobin 6.6 grams, 45 per cent; red blood cells 2,430,000; color index 0.9; white blood cells 3,450; segmented neutrophils 70 per cent, lymphocytes 29 per cent, monocytes 1 per cent; icterus index 11.4; hematocrit 0.20; reticulocyte count 0.4 per cent; no gastric free hydrochloric acid following histamine; stool negative for occult blood. The day after admission a gastrointestinal series was negative, whereas a barium enema showed an area of constriction at the rectosigmoid. Four days later the barium enema was repeated and showed an area of constriction in the sigmoid colon in which normal mucosal markings were present. The constriction was not constant. Sigmoidoscopic examination was negative. The patient was given ferrous sulphate and his reticulocyte count rose to 1.7 per cent without other improvement. Clinical impression at this time was gastrointestinal malignancy. The day before puncture was done, his hemoglobin was 8.2 grams, 56 per cent; red blood cells 2,310,000; color index 1.2; hematocrit 0.24; mean corpuscular volume 104 cubic micra; mean corpuscular hemoglobin 35 micromicrograms; mean corpuscular hemoglobin concentration 33 per cent. On the thirteenth day after admission a sternal marrow puncture revealed a hyperplastic marrow in which the dominant cell was a polychromatic megaloblast; the red cell line was megaloblastic and hyperplastic and the myeloid-erythroid ratio was 1:2, a reversal of normal; the granulocytic line of cells showed a left shift, with myelocytes predominating; macropolycytes were present in the marrow and the beginning of nuclear deformity could be seen in the myelocyte stage (table 4). Diagnosis: pernicious anemia. The patient was given liver extract parenterally, the reticulocytes rose to 6 per cent on the sixth day subsequently, and he was eventually discharged feeling well, with hemoglobin 10.7 grams, 76 per cent; red blood cells 3,850,000; and color index 1.0. Nine months later, after receiving parenteral liver every two weeks, the hemoglobin was 15.3 grams, 104 per cent; red blood cells 5,100,000.

This case did not show typical blood findings or central nervous system changes which are characteristic of pernicious anemia.\* The roentgenographic findings were confusing. It is conceivable that liver therapy might have been tried as a therapeutic test. However, a positive diagnosis was reached quickly by means of the puncture. If this had been done earlier when the etiology of the anemia was first in doubt the period of hospitalization and uncertainty would have been shortened appreciably.

\* Since this series of cases was closed, we have seen another case of severe pernicious anemia in a 35-year-old white woman in whom there was also no involvement of the central nervous system and in whom the peripheral blood indicated a hypochromic type of anemia. The laboratory findings on the peripheral blood of this case were: hemoglobin 3.56 grams, 24 per cent; red blood cells 1,400,000; color index 0.8; hematocrit 0.10; mean corpuscular volume 75 cubic micra; mean corpuscular hemoglobin 27 micrograms; mean corpuscular hemoglobin concentration 35.6 per cent. These findings seemed so incredible in view of a diagnosis of pernicious anemia which had been made from sternal puncture that they were repeated twice by each of two observers with identical results. The patient recovered with liver extract therapy. Wintrobe<sup>10</sup> has recently reported two similar cases.

## II. *Punctures enabling a more rapid diagnosis.*

*Case 8.* A 22-year-old female had been given 10 grains of prontosil (in 1937) every six hours for two days because of a sore throat. Weakness, headache, nausea and vomiting followed. On the fourth day there was a definite jaundice which cleared up on the sixth day. The liver was enlarged. Eight days after the onset of her illness she entered the hospital complaining of weakness, nausea, and vomiting. The patient was extremely pale, underdeveloped and undernourished. There were small palpable lymph nodes in both posterior cervical chains and in the right axilla and inguinal region. The spleen was very firm and palpable one finger's-breadth below the costal margin.

Laboratory data: hemoglobin 2.3 grams, 16 per cent; red blood cells 830,000; white blood cells 17,600; segmented neutrophils and bands 63 per cent, myelocytes 4 per cent, eosinophils 5 per cent, basophils 4 per cent, monocytes 5 per cent, lymphocytes 19 per cent; a few myeloblasts and nucleated red blood cells were present in the smear; reticulocytes 4.5 per cent; icterus index 10; urine negative for bile and urobilinogen normal; the feces contained bile, were negative to the benzidine test, and no ova or parasites were found. The question was whether this was a leukemoid reaction following an acute hemolytic anemia or an acute leukemia. Sternal puncture showed a marrow within the normal range of cellularity, but the predominating cell was a basophilic normoblast. The red cell series was markedly hyperplastic, the myeloid-erythroid ratio being 2:3; a few megaloblasts were seen; the white cell series showed a left shift, but no evidence of leukemia. Diagnosis: leukemoid reaction to acute hemolytic anemia. The patient was transfused and recovered.

This sternal puncture was done the morning after admission to the hospital. All suspicion of a malignant process was dispelled within 24 hours after admission.

*Case 9.* A 17-year-old white male with a history of epistaxis in childhood three weeks before admission had a nose bleed every one to two days which required packing to stop it. There was occasional nausea and vomiting associated with bleeding. Small purpuric spots had been noted on the forearms for four months. Gingival bleeding and ecchymoses resulted from slight trauma. His father had suffered frequently from epistaxis in childhood. Examination showed a temperature of 100.5° F., pallor, petechiae on the buccal mucosa, liver palpable two fingers'-breadth below the costal margin, spleen not palpable, slight general lymphadenopathy. Laboratory data: hemoglobin 6.5 grams, 44 per cent; red blood cells 2,230,000; color index 1.0; total nucleated cell count 7,400, of which 51 per cent were nucleated red cells, and the white blood cells, therefore, 3,600; segmented neutrophils 46 per cent, band 7 per cent, metamyelocytes 7 per cent, myelocytes 8 per cent, monocytes 8 per cent, lymphocytes 24 per cent; platelet count 140,000. The red cells in the smear showed anisocytosis, poikilocytosis, basophilic stippling, polychromasia, and many megaloblasts were present as well as normoblasts. Bleeding time was 8.5 minutes; clotting time of venous blood, 6 minutes; no clot retraction; hematocrit 0.19; volume index 1.9; mean corpuscular volume 85.4 cubic micra; mean corpuscular hemoglobin 27 micromicrograms; mean corpuscular hemoglobin concentration 32.5 per cent. Fragility test: hemolysis began at 0.42 per cent and was complete at 0.34 per cent; Rumpel-Leeds test was negative. The clinical impression was purpura hemorrhagica. Sternal puncture was done four days after admission. The marrow revealed markedly increased cellularity with the myeloblast predominating. The neutrophilic series was shifted far to the left with myeloblasts, promyelocytes, and myelocytes present in greatly increased numbers, whereas mature neutrophils were rare. Red cell formation was increased, the myeloid-erythroid ratio being 1:1. Diagnosis: acute myelogenous leukemia in subleukemic stage. The patient gradually failed and six weeks after puncture the total white cell count rose to 30,000 cells of which 27 per cent were myeloblasts, a

frankly leukemic blood picture. At this stage the patient showed marked gingival swelling so that the teeth were buried in the tissue; the monocyte count rose to 19 per cent. The patient died at home and no autopsy was done.

The correct diagnosis could ultimately have been made in this case without puncture. As a matter of fact, it is felt that sufficiently expert examination of the first blood smear made on this patient would have revealed the nature of his illness. However, under the circumstances, the puncture enabled the consultant to visualize the actual condition of the patient's hematopoietic system, and permitted an earlier diagnosis and a more accurate prognosis than would otherwise have been possible.

### *III. Punctures confirming diagnosis in doubtful cases.*

There were four such cases in our series. In all of them diagnosis was almost certain, and yet there were puzzling features about each case which prevented a definite conclusion. Two of these histories are given.

*Case 10.* A white male 53 years of age complained of a loss of 35 pounds in six months and a mass in the left upper quadrant of the abdomen, which he noticed himself. Examination showed splenomegaly but no lymphadenopathy and was otherwise entirely negative. Laboratory data: hemoglobin 17.5 grams, 119 per cent; red blood cells 5,940,000; white blood cells 22,400; segmented neutrophils 21 per cent, monocytes 4 per cent, lymphocytes 75 per cent; platelets were present but reduced in number; the majority of lymphocytes were small and of a mature type. A diagnosis of chronic lymphatic leukemia would have been indicated except for the complete absence of any enlargement of the lymph nodes on repeated examination. Sternal puncture showed a marrow within the normal range of cellularity, but the predominant cell was a small lymphocyte. Both the granulocytic and erythroid series showed all the stages normally found in the marrow in the proper proportion. A differential count of 500 of the marrow cells showed lymphocytes 74.2 per cent, 47.3 per cent of which were small and 26.9 per cent intermediate in size. A few lymphoblasts were seen in the marrow smears during study. Diagnosis: chronic lymphatic leukemia.

*Case 11.* A 57-year-old white male complained of constipation, loss of weight, anorexia, and discomfort in the lower abdomen for six weeks. For the five days before admission he had had a sore throat and tongue. Examination showed round, elevated white spots over the pharynx, faucial pillars and soft palate; the edges of the tongue were covered with a heavy, white slimy coating, and papillae were absent from the anterior portion. The spleen was palpable, and what was considered to be the liver (see below) was palpable five fingers'-breadth below the costal margin. There was no lymphadenopathy. Laboratory data: hemoglobin 11 grams, 75 per cent; red blood cells 4,500,000; white blood cells 28,500; segmented neutrophils 75 per cent, bands 14 per cent, metamyelocytes 2 per cent, monocytes 2 per cent, lymphocytes 7 per cent; basal metabolic rate, urine, stool, gastrointestinal series negative; cholelithiasis by roentgenogram; gastric free hydrochloric acid present. Three days later: white blood cells 45,700; segmented neutrophils 70 per cent, bands 18 per cent, metamyelocytes 3 per cent, myelocytes 2 per cent, monocytes 2 per cent, lymphocytes 5 per cent. A diagnosis of chronic myelogenous leukemia was made but because of the small number of immature cells present in the blood, a leukemoid reaction could not be ruled out. Sternal puncture revealed an extremely cellular marrow (of leukemic degree) in which the neutrophilic band form was the predominant cell but myelocytes and promyelocytes were also greatly increased in proportion to normal. The diagnosis of chronic myelogenous leukemia was confirmed. The patient was discharged from the hospital, but returned again four weeks later with a red blood count of only 2,700,000; the total white blood count remained the same as before.

but 5 per cent myeloblasts were now present in the peripheral blood. One week after the second admission, the patient died, and at autopsy it was found that the mass in the right upper quadrant was not liver but a large hypernephroma which, however, had not yet metastasized. The bone marrow and the spleen showed changes typical of myelogenous leukemia, but no leukemic infiltrations were found in any other organ.

#### *IV. Punctures aiding differential diagnosis.*

Twenty-six of our 74 cases in which there was a clinical indication for doing the puncture fall into this category, as they showed non-specific myelograms. Although a diagnosis usually cannot be made from punctures which give negative results, they are in many instances of help in differential diagnosis, and may present certain information which cannot be obtained in any other way. Too much reliance should not be placed on them, the results must be interpreted guardedly and only in relation to the general clinical picture. The usefulness of the method in differential diagnosis is shown in the following five cases.

*Case 12.* A 57-year-old white male had had a resection of a carcinoma of the ascending colon. Five days after operation purpuric spots on the skin, epistaxis and melena appeared, and were accompanied by pallor. Laboratory data: hemoglobin 4.3 grams, 29 per cent; red blood cells 1,380,000; white blood cells 4,640; segmented neutrophils 35 per cent, bands 23 per cent, metamyelocytes 2 per cent, eosinophils 3 per cent, monocytes 11 per cent, lymphocytes 26 per cent; platelets, 31,000; bleeding time, 25 minutes; coagulation time, 12 minutes (venous blood); no clot retraction in 24 hours; reticulocyte count 1 per cent. Purpura hemorrhagica was strongly suspected by the surgeon who considered the advisability of doing a splenectomy. Sternal puncture showed an almost complete absence of marrow cells, although marrow fluid was obtained easily. This fact tended to rule out purpura hemorrhagica, because in this disease marrow findings are essentially normal, and suggested that an aplasia of the marrow was present. A trephine biopsy of the marrow would have been done except for the critical condition of the patient. By deduction it was felt that the most logical cause for marrow aplasia in this patient was metastatic carcinoma. Autopsy of this case showed widespread carcinomatosis with replacement of marrow tissue. It is interesting that with such metastases present no malignant cells were found in the fluid obtained by puncture.

*Case 13.* A white male 33 years of age had a marked hypochromic anemia for which no cause could be discovered. A sternal puncture was requested for added information because the etiology of the anemia could not be determined. Sternal puncture showed hyperplasia of the red cell series in a marrow with a normal degree of cellularity. A diagnosis of iron deficiency anemia was made and iron therapy was carried out successfully with assurance that the more malignant diseases considered were not present.

*Case 14.* A 21-year-old white male had suffered from a condition diagnosed twice as infectious mononucleosis, for a period of three years, with only short periods of well-being. He again showed lymphadenopathy and a typical blood picture of mononucleosis. Since no case of this disease had been reported lasting for such a long time, it was felt that lymphatic leukemia had to be considered. The sternal marrow, though of increased cellularity, was normal cytologically, so that a diagnosis of chronic lymphatic leukemia was not supported.



*Case 15.* An 80-year-old white female had enlarged non-tender lymph nodes in the left neck, both axillae and both inguinal regions. The liver and spleen were definitely palpable one finger's-breadth and two fingers'-breadth below the costal margin respectively. There was a definite but moderate hypochromic anemia but the total white blood cell count was normal and no immature cells were present. The sternal marrow was normal except for a slight lymphocytosis. It was then felt that lymphatic leukemia was probably not present. Biopsy of a gland was not desired in this patient by the attending physician so roentgen-ray therapy was advised. Marked temporary improvement occurred with this treatment.

*Case 16.* A white male 64 years of age was found to have anemia but nothing abnormal in his white cell count, after an enlarged spleen palpable three centimeters below the costal margin was discovered. He had been chronically fatigued, and felt continually sleepy for one and a half years. For two months he had had lower abdominal pains but gastrointestinal roentgenograms were negative. A history of habitual use of Bromo-Seltzer over a period of four to five years was obtained. Undernutrition and a dusky pallor with a cyanotic tinge to the mucous membranes were noted. The blood bromides were over 100 mg. per cent, with no methemoglobin present. The attending physician's impression was aleukemic leukemia. Sternal puncture showed a normal cellularity in the smears, with some left shift in the neutrophilic series, the predominating cell being, however, the band form. The diagnosis was chronic acetanilid and bromide intoxication with splenomegaly. The sternal marrow examination was felt to be of definite aid in the differential diagnosis of this case.

TABLE IV  
Form Used in Making Reports on Sternal Punctures

ALBANY HOSPITAL  
MYELOGRAM

Name: Doe, John  
Hosp. No. 55,963

Date: June 18, 1940

Findings	Normal Marrow	Patient's Marrow
Cellularity	Grade 1, 2, or 3 (usually 2)	Grade 3
Predominant Cell	Segmented or band neutrophile	Polychromatophilic megaloblast
Neutrophilic Series	Complete series; few early forms	Shifted to left, myelocytes predominating
Erythroid Series	Normoblastic; few early forms	Megaloblastic hyperplasia; many early forms; normoblasts scanty
Myeloid-Erythroid Ratio	3 : 1 to 50 : 1	1 : 2
Reticulocyte Count	0.5% to 4.0%	1%
Lymphocytic Series	Small number of mature forms	Normal
Monocytic Series	Small number	Normal
Other Cells	Small numbers of plasma cells, megakaryocytes, reticulum cells, macrophages, cells in mitosis, eosinophiles, basophiles	Macropolycytes present

*Discussion:*

This marrow is almost completely megaloblastic. The myeloid-erythroid ratio is reversed, indicating a marked hyperplasia of the erythroid elements. The beginning of nuclear deformity resulting in the formation of macropolycytes can be seen in the myelocyte stage.

*Diagnosis:* Megaloblastic marrow typical of pernicious anemia in relapse.

## MYELOGRAM

The results of the sternal punctures are reported by a form (table 4) called a "myelogram," which is in essence a brief tabulated description of the marrow picture compared to normal marrow. In our experience, this form of report is much more satisfactory than a differential count or a cytological description of the puncture findings, as both the count and the description are unintelligible to persons not particularly interested in hematology. Total and differential counts of marrow cells in the puncture fluid are not essential for practical interpretation, although occasionally a differential count is necessary for the purpose of establishing the predominant cell type. The facts on which the normal myelogram is based have been already discussed in the section on cytology.

In studying the literature, as well as our own data, it became at once apparent that sternal puncture findings fall into two groups: (1) myelograms which are typical of a particular disease, and which when present are so reliable as to either indicate the diagnosis or to be actually pathognomonic. These may be termed specific or typical myelograms; (2) myelograms which are non-specific and which may occur in a variety of conditions and be useful in association with the complete clinical picture, but which alone are without value for diagnostic purposes. Specific myelograms are present in the following conditions:

1. Leukemia, especially acute and leukopenic leukemia.
2. Megaloblastic marrow, present typically in pernicious anemia in relapse, achrestic anemia, and sprue.
3. Agranulocytosis in the arrested marrow stage.
4. Neoplasms: multiple myeloma and metastatic malignancies, especially carcinoma.
5. Lipoid histiocytosis.
6. Malaria.
7. Leishmaniasis (kala azar).

It is not to be assumed that all of the above conditions will always give diagnostic marrow pictures, but when specific findings are present they indicate the diagnosis. Bizarre cases are encountered in which the picture is doubtful, confusing, or possibly even negative. The absence of a typical myelogram cannot be relied upon absolutely to rule out a disease in differential diagnosis, because of the possibility of an error in sampling and atypical variations in pathology. Negative findings can, however, be extremely useful in some instances, as is shown by cases 5, 13, 14, and 16 of this paper.

In chronic myeloid leukemias, the peripheral blood findings are usually adequate for diagnosis without investigation of the marrow. Sternal puncture is, however, indicated in cases of chronic leukemia in a leukopenic phase, in early cases in which peripheral blood studies are inconclusive, and in cer-

tain cases in which conflicting data throw doubt on the diagnosis. Incontestable evidence of myeloid hyperplasia is, however, necessary for a diagnosis when the peripheral blood picture is not characteristic, and there must be a marked increase in the younger types of cells, namely the myelocytes, promyelocytes, and myeloblasts. These marrows are usually of Grade 4 cellularity. Eosinophilic and basophilic myelocytes and promyelocytes may also be markedly increased over normal.

Large numbers of myeloblasts, with either this cell or the promyelocyte as the predominating type, are necessary for a diagnosis of acute myelogenous leukemia. The designation of an arbitrary fixed percentage of a cell type above which leukemia is stated to be present, as has been suggested by some authors, seems to us in the present state of knowledge extremely unwarranted.

In chronic lymphatic leukemia the bone marrow is replaced by lymphatic tissue, and most of the cells seen in the puncture fluid are of the mature type, though occasional lymphoblasts are present. In acute lymphatic leukemia, however, lymphoblasts are the predominating cells. This transformation of the marrow may occur with a leukopenic peripheral blood picture. In certain other diseases, such as infectious mononucleosis, there is a relatively high percentage of lymphocytes in the peripheral blood, and accordingly a relatively high lymphocyte count will occur in the marrow, but the marrow is obviously not being replaced by lymphocytes.

In acute monocytic leukemia the normal marrow is replaced by monocytic cells and large numbers of premonocytes and monoblasts are found. This may also occur when the peripheral blood picture is leukopenic.

It must be borne in mind that accompanying the conditions which produce leukemoid reactions in the peripheral blood, such as infection, acute hemolysis and acute hemorrhage, a hyperplasia and a "left shift" of the leukocytes may occur in the bone marrow. As a matter of fact, the peripheral blood picture is merely a reflection of the change in the marrow. The percentage of younger forms of the neutrophilic series increases, but the increase is mostly in the bands and metamyelocytes, and the myeloblasts are not affected in the small number of cases we have examined. Sometimes, however, a leukocytosis does not occur in the peripheral blood and the "left shift" may be present in spite of the leukopenia. It is felt that under these circumstances although the marrow is hyperplastic, delivery of cells to the peripheral blood is defective. The eosinophilic marrow cells are not affected unless an eosinophilic leukocytosis is also present in the peripheral blood.

In agranulocytosis, two types of marrow may be found: (1) the more mature forms of the neutrophilic series are absent, which may be a "maturation arrest," but all the younger forms are present and may even be increased in number; and (2) a so-called "empty" marrow in which all granulocytic cells are absent and only lymphocytes, plasma cells and small normoblasts are present in the smears. In the latter type, in some cases, very few cells of any

kind are present in the smears. Curiously, in three of the five cases of this disease we studied the erythroid series was represented only by small normoblasts. The significance of this is not evident. In our small series of cases, a "maturation arrest" of the marrow was indicative of a more favorable prognosis. In empty marrows, the prognosis was bad. A "maturation arrest" in the marrow is a typical myelogram, and is diagnostic, but in the marrows showing a complete absence of granulocytic cells a trephine biopsy must be done to avoid confusion with true aplastic anemia and myelophthisic conditions, or the diagnosis must be based on the associated clinical picture, which is not always reliable.

The recognition of megaloblastic marrow is of great importance in the diagnosis of pernicious anemia. The presence of megaloblastic cells in a case of anemia, without other explanation for the anemia (such as leukemia or sprue) and in the presence of true achlorhydria is sufficiently diagnostic of pernicious anemia to indicate a therapeutic test with a large dosage of liver extract, even though the peripheral blood studies are inconclusive. The marrow findings are identical in pernicious anemia and sprue, but the latter disease is of course characterized by a quite different clinical picture. These two diseases, in addition to the abnormal variety of red cells, also have pathological changes in the neutrophile series. These consist of abnormally early maturation changes in the nucleus, so that it is possible to find promyelocytes which have the nuclear characteristics of band forms.<sup>7</sup> The continuation of these changes results in the formation of the "hypersegmented pernicious anemia neutrophile" or macropolycyte, which is sometimes found in the peripheral blood and which may have as many as 15 lobes in the segmented nucleus. Following the injection of liver extract, as is well known, the bone marrow and the peripheral blood return to normal. The beginning of the transformation may be apparent in the marrow 12 hours after injection, it is said. The change is accomplished by the rapid maturation of the megaloblastic cells to non-nucleated megalocytes; they are replaced in the marrow by normoblastic cells which then mature to normocytes, and it is only at this time that the Price-Jones curve returns to normal. There is no evidence that megaloblastic cells ever transform to normoblasts. The abnormal neutrophilic cells mature and are replaced by normal cells in some but not in all cases. Achrestic anemia also has a predominantly megaloblastic marrow, and the peripheral blood picture may be identical with pernicious anemia but free hydrochloric acid is secreted by the stomach and proper response to liver extract does not occur. Megaloblasts in smaller numbers were also found in other conditions in our series of cases: in leukemia, acute hemolytic anemia, and in one clinically typical case of acute "aplastic" anemia in a young adult. In these latter conditions, however, the normoblastic type of erythropoiesis was the predominant form of red cell production.

In our cases, neoplasms have been studied only as they have entered into

the differential diagnosis of hematological disorders. It is felt that other methods of investigation are superior to sternal puncture in diagnosing malignancies, with the exception of multiple myeloma. No tumor cells were found in the puncture fluid in any of our cases, except in our one case of the latter disease.

In the one case of lipoid histiocytosis which we were able to study, no foam cells were found in the puncture fluid. They were found, however, in a biopsied lymph node. This case illustrated the dangers of ruling out a disease because of negative puncture findings.

Malaria and kala-azar have not occurred among the cases we were able to study. They are listed among the specific myelograms because other investigators have shown that sternal puncture is often of help in their diagnosis. Sternal marrow, obtained by trephine, was first used in the diagnosis of the latter two diseases by Seyfarth.<sup>17</sup> In kala-azar, sternal puncture is preferred to splenic puncture as it is less dangerous to the patient. Not all of the investigators of the question are in agreement, but it is said that malaria can be diagnosed from sternal puncture samples when the peripheral blood is negative, a finding which may be of importance in tropical medicine.

All other diseases so far studied have a nonspecific marrow picture. The nontypical or nonspecific myelograms, though they do not give the diagnosis, are often of great interest and usefulness in relation to the general clinical picture. Polycythemia, hypochromic, hemolytic and aplastic anemias, and myelophthisic anemia such as occurs in Hodgkin's disease and reticulosis, are among the diseases giving marrow pictures which are not diagnostic. Aplastic anemia is placed in this category because it may show a marrow condition upon puncture which varies from complete aplasia to extreme hyperplasia. One of the cases of this disease which we studied was a clinically typical case of acute idiopathic "aplastic" anemia in a young adult, but the marrow was of normal cellularity with a normal myeloid-erythroid ratio; there was a left shift in the neutrophilic series and also in the erythroid series, and some megaloblastic red cell formation was present. The presence of megaloblastic cells in this marrow is of considerable scientific interest, as it has been previously reported<sup>8, 15</sup> that megaloblasts do not occur in this type of case. In the true aplastic anemias, such as our second case of this disease, complete aplasia of the marrow is present, but a trephine biopsy is necessary after the sternal puncture has been done in order to be sure that the failure to aspirate any cells is not due to a replacement process which resists aspiration.

#### CLINICAL INDICATIONS FOR STERNAL PUNCTURE

After a thorough examination of the case histories and the evaluation of the results of the punctures in our series, the following criteria were selected as indications for the practical use of the sternal puncture method

of marrow biopsy. A sternal puncture should always be done when (1) the diagnosis is in doubt and a disease usually showing a typical myelogram cannot be excluded, for example; an agranulocytosis in which there is the possibility of aleukemic leukemia; (2) the etiology of the peripheral blood findings is obscure: "aplastic" anemia or "idiopathic" anemia; (3) other means of diagnosis short of surgical biopsy have failed. In addition, a sternal puncture *may* be done to (1) save time if a specific marrow picture is likely to be present; (2) obtain information concerning prognosis; (3) determine response to treatment, as in a pernicious anemia which does not seem to benefit from liver extract therapy; (4) determine the type of a "stem cell" leukemia when this cannot be done with certainty from the peripheral blood.

### CONCLUSIONS

We find that sternal puncture, when used on cases in which it is definitely indicated, is an extremely valuable and practical diagnostic method. Elaborate technics of handling and studying the marrow samples, however valuable from a research standpoint, are unnecessary for clinical use of the method. Under actual working conditions 65 per cent of our indicated punctures gave information which was of clinical value, and the diagnosis was made by means of the puncture in 16.2 per cent of our 74 indicated cases. Sternal puncture cannot be substituted for thorough clinical investigation of the patient. Indeed, the more thorough the work-up of the patient, the easier and more valuable is the interpretation of the puncture. Most diseases, unfortunately, do not show specific changes in the marrow from which a definite diagnosis can be made, but much clinically valuable information can be obtained which is of aid in the differential diagnosis and subsequent handling of the patient. Diagnoses should be made only from specific myelograms, and a negative result does not absolutely preclude the presence of a given disease, because of the possibility of not having secured a representative sample of marrow and of atypical variations in the pathologic lesions of the disease. Punctures which yield no marrow cells upon aspiration should be followed by a trephine biopsy, if the diagnosis can be reached in no other way, and no contraindication is present.

### SUMMARY

1. Sternal marrow puncture is an extremely useful and practical procedure in the study of diseases of the blood and in cases in which the possibility of such diseases enters into the differential diagnosis. It should, however, be used only on definite indications.
2. In our series of 140 cases, 65 per cent of the 74 indicated punctures gave information of clinical value, and the actual diagnosis was made in 16.2 per cent when this was impossible by any other method short of biopsy.

3. Diagnosis can be made with certainty only when a typical or specific myelogram is present.
4. Negative findings must be interpreted with caution and fully correlated with the entire clinical picture.
5. No diagnosis can be made from nonspecific myelograms, but they sometimes yield information of great clinical value.
6. Sternal punctures may also be clinically useful for rapid diagnosis, confirmation, prognosis and for follow-up of treatment.

## BIBLIOGRAPHY

1. ARINKIN, M. I.: Methodology of examining bone marrow in living patients with hemato-poietic disease, *Vestnick. khir.*, 1927, x, 57 (quoted from VOGEL, ERF and ROSEN-THAL<sup>6</sup>).
2. ARINKIN, M. I.: Intravital Untersuchungsmethodik des Knochenmarks, *Folia hæmatol.*, 1929, xxxviii, 233-240.
3. NORDENSON, N. G.: Studies on bone marrow from sternal puncture, 1935, Bortzells, Esselte, Stockholm.
4. SEGERDAHL, E.: Ueber Sternalpunktion, *Acta med. Scandinav.*, 1935, Suppl. lxiv, 1-162.
5. YOUNG, R. H., and OSGOOD, E. E.: Sternal marrow aspirated during life, *Arch. Int. Med.*, 1935, lv, 186-204.
6. VOGEL, P., ERF, L. A., and ROSENTHAL, N.: Hematological observations on bone marrow obtained by sternal puncture, *Am. Jr. Clin. Path.*, 1937, vii, 436-447 and 498-515.
7. JONES, O. P.: Cytology of pathologic marrow cells with special reference to bone-marrow biopsies, *Downey's Handbook of Hematology*, 1938, iii, 2045-2101.
8. SCOTT, R. B.: Sternal puncture in diagnosis of diseases of blood forming organs, *Quart. Jr. Med.*, 1939, viii, 127-172.
9. KANDEL, E. V., and LEROY, G. V.: Limitations of biopsy of sternal marrow, *Arch. Int. Med.*, 1939, lxiv, 121-135.
10. FALCONER, E. H., and LEONARD, M. E.: The value of sternal marrow aspirations as a method of bone marrow biopsy, *Ann. Int. Med.*, 1941, xv, 446-458.
11. MENDELL, T. H., MERANZE, D. R., and MERANZE, T.: The clinical value of sternal bone marrow puncture, *Ann. Int. Med.*, 1942, xvi, 1180-1196.
12. THOMPSON, W. R.: Biological applications of normal range and associated significance tests in ignorance of original distribution forms, *Ann. Math. Soc.*, 1938, ix, 281-287.
13. TEMPKA, T.: Das Problem der Biermerschen perniziösen Anämie als klinische Einheit, *Wien. med. Wchnschr.*, 1935, lxxxv, 85-87, 116-118, 148-150.
14. SCHWIND, J. L.: A study of the megaloblast problem with the supravital method, *Anat. Rec.*, 1941, lxxix Suppl., 55.
15. JONES, O. P.: Morphologic, physiologic, chemical and biologic distinction of megaloblasts, *Arch. Path.*, 1943, xxxv, 752-775.
16. WINTROBE, M. M.: *Clinical hematology*, 1942, Lea and Febiger, Philadelphia.
17. SEYFARTH, C.: Die Sternuntrepanation, eine einfache Methode zur diagnostischen Entnahme von Knochenmark bei Lebenden, *Deutsch. med. Wchnschr.*, 1923, xlix, 180-181.

# KALA AZAR: A REVIEW OF ITS INCIDENCE AND EPIDEMIOLOGY IN CHINA AND CLINICAL OBSERVATIONS ON 585 CASES \*

By FREDERICK G. SCOVEL, M.D., F.A.C.P., *Rochester, New York*

THIS paper has chiefly a threefold purpose: to report chronologically on the incidence of kala azar in China, to present an up-to-date summary of what has been done in China to determine how this disease is spread, and to offer a study of some of the cases seen by us by presenting tables and observations dealing with symptoms, physical signs, laboratory data and responses to therapy.

## HISTORY

There are no records or descriptions of a clinical syndrome resembling kala azar in old Chinese literature, as is the case with malaria.† It is therefore impossible to determine how long the disease has existed in this country. If the presence of enlarged spleens in children can be interpreted as evidence, it was present for many decades before its identity was determined.

Very little is known regarding the time and mode of ingress of kala azar into China. Two possible routes of entry have been suggested. One is by way of trade routes from India across the Himalaya mountains and north through Tibet. The other is by sea, also probably from India. The port of Haichow, which has been an important trading center for many years, could reasonably be considered as a portal of entry and source for the infection of the districts where kala azar is most prevalent.

## DISTRIBUTION

Kala azar is endemic throughout the whole of China north of the Yangtze River, extending west to Szechuan and north to Manchuria. However, it is most prevalent in Hopei, Manchuria, Anhwei and Kiangsu along the old Yellow River bed. A total of 5,000 cases was treated annually in three hospitals in this last area. Sporadic cases are only occasionally reported in southern China.

Our earliest record is from a letter by Rev. J. S. McIlvaine written from Tsining, Shantung, on February 26, 1880 which reads, "A few days since I was applied to in regard to a case of 'pe' (spleen), a common disease here, which I cannot make out in

\* This article was received for publication October 31, 1941, but its appearance was delayed because of the protracted internment of the author in China by the Japanese. Since his release and return to the United States in December 1943, the article has been revised to give consideration to more recent discoveries, particularly regarding the mode of transmission of the disease.

From the Bachman Hunter Memorial Hospital, Tsining, Shantung, China, of which the author was superintendent.

† From a personal letter from Dr. Hoeppli of Peiping Union Medical College.



*Flint's Medicine.* It is a hard growth which gradually extends over the whole abdomen. They say there is no liquid effusion. . . . The bowels are not interfered with nor is there pain, but when the abdomen is all hardened the person dies." \*

In 1887 and 1888 Coltman<sup>1</sup> reported cases of enlarged spleen seen in the Tsinan, Shantung, dispensary. It was refractory to all forms of attempted treatment. The patients also exhibited "pearly conjunctiva, pale flabby tongue, gradual loss of flesh

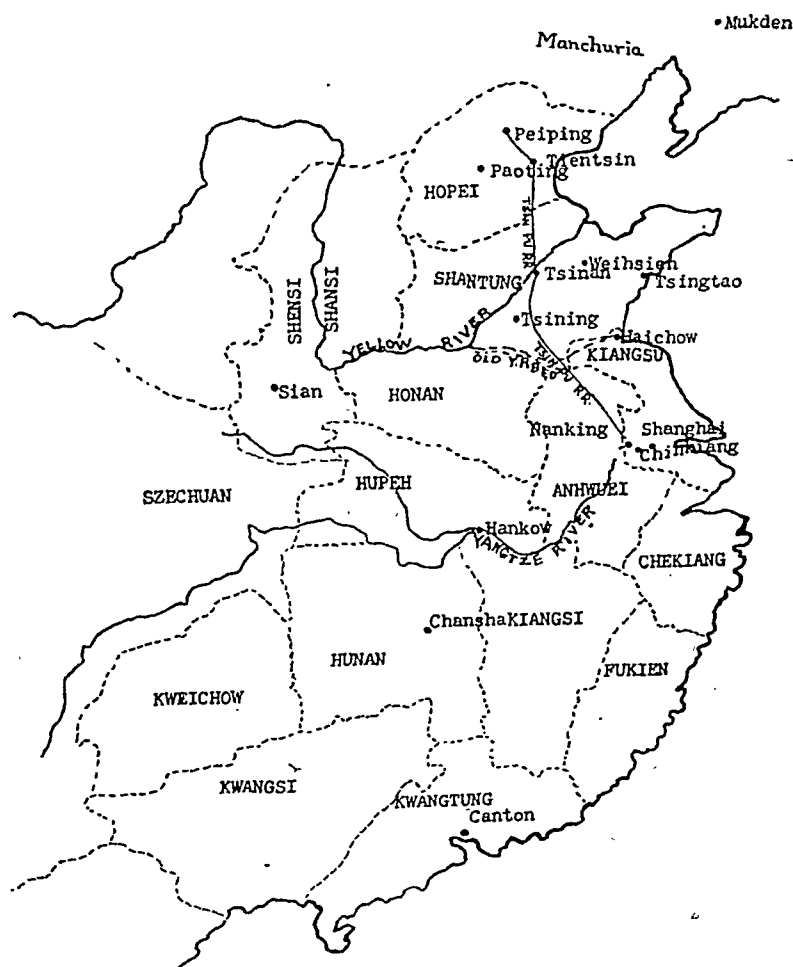


FIG. 1.

and ultimate death." The first two cases of kala azar recognized in China were in a German soldier who died of it in Peiping in 1900 and in a native from Hankow in 1905. Young<sup>2</sup> mentioned these, and in addition subsequent cases in Tsingtao, Tientsin and Kiukiang, all seen before 1910.

In 1911 Aspland<sup>3</sup> reported from Peiping that kala azar was frequently encountered in the northern provinces, but occurred only in children. Jeffrys and Maxwell<sup>4</sup> stated that in 1911 it was common over the greater part of China north of the Yangtze River and the provinces on the south, but absent farther south. Also in 1911 and 1912 Cochran<sup>5, 6</sup> described the disease in 12 centers in north China and reported a number of infections in children whose disease had been diagnosed by

\* Taken from "On the Shantung Front"—J. J. Heeren, p. 204.

liver and spleen punctures. Reed <sup>7</sup> reported a case from Ch'angsha the following year, and mentioned that it seemed to have been contracted from the bites of bedbugs. Wylie <sup>8</sup> observed 35 in-patients in Paoting, Hopei, from 1919-1920. Most of them came from the flooded districts in the southeast.

Young <sup>2</sup> in 1923 reported a total of 25 kala azar areas, adding 13 to those already mentioned by Cochran. A Weihsien report <sup>9, 10</sup> states that in 1922 and 1923 kala azar was prevalent in east central Shantung, although recently its incidence has decreased. King <sup>11</sup> found it in Kansu. Taylor <sup>12, 13</sup> reported an average of 9 to 10 cases a year in Mukden from 1917 to 1931, coming from districts 200 miles west and 100 miles southwest, as well as from Shantung. Morris <sup>14</sup> reported a case from a district in Kiangsu where the disease had not been encountered previously. Also in 1931 Sturton <sup>15</sup> found it in Chekiang. Two years later <sup>16</sup> it was identified in Kiangsi, spreading north along the Tsinpu R. R. and opening up a new area (Nanchuang) where it had become epidemic. In Chinchiang 5,000 cases were seen from April 1932 to April 1933. From here it extended south.

In 1934 Fan and Scott <sup>17</sup> reported 302 kala azar cases among 5,800 in-patients in Tsinan, Shantung, 57 of whom had noma. Du and Best <sup>18</sup> gave a case report on a patient seen in Kansu two years later. Schretzenmayr, Chu and Tsen found 84 cases in Canton in 1938. Nearly all of these were soldiers or officers, and it seemed that they had contracted the infection in the north.<sup>18</sup> Clow <sup>19</sup> in 1941 found 196 cases in Sian, Shensi, 93 per cent of which were infected locally.

Many Chinese have asserted that kala azar follows in the wake of famine, flood and war. These observations are borne out by its prevalence in the north of China between Nanking and Peiping where almost from time immemorial one catastrophe after another has repeatedly ravaged the country. Wylie <sup>8</sup> reported that his 35 patients came from flooded districts. A review of the literature on the incidence of kala azar in north China was made in 1942 and 1943, and it revealed that there had been a marked increase since the outbreak of Japanese hostilities. But it is practically unknown in the south of China where crops are a surer venture and where wars do not so frequently penetrate. However, its infrequency may be due to the absence of the transmitting vector, or reservoir host.

In our district of southern Shantung kala azar remained endemic until the end of 1937. Prior to this we rarely saw more than 8 cases a year, although 110 miles to the east a hospital had continually been having large clinics since its opening several decades ago. Then after the onset of the Japanese invasion the number of our cases suddenly increased.

### INCIDENCE

Although kala azar frequently does occur in the cities it is usually a disease of the villages. Many families will often have one courtyard, but usually there will be only one case present. However occasionally we found more than one patient in a family. In the larger cities it is usually found only in the outskirts where the sandfly exists. In general it is a disease of the poorer classes, but this is probably due to the location of their abodes rather than to social status.

"The number of cases presenting themselves for treatment is not only dependent upon the incidence of the disease in the community, but is also influenced by the efficacy of the therapeutic agent, the price of the treatment and the accessibility of the hospital." \*

The 585 patients reported in this article were seen from January 1, 1940 to June 30, 1941 and included both in-patients and out-patients. The incidence of the disease by age and sex is recorded in table 1 and corresponds

TABLE I  
Age and Sex

	1-2	3-5	6-10	11-15	16-20	21-25	26-30	31-40	41-50	over	Total
M	6	55	152	116	76	48	30	39	8	0	530
F	4	5	13	18	3	4	3	3	2	0	55
Total	10	60	165	134	79	52	33	42	10	0	585

to the observations of others. Perhaps there is a higher incidence above the age of 20 than is usually noted. The low proportion of female patients is of interest merely in demonstrating a preference for first treating the opposite sex. Therefore it is of no scientific interest, as an accurate record of the comparative incidence of the disease in the two sexes could be obtained only by a house to house canvass in the infested villages.

A record was made of the estimated month of onset in 488 patients. The others were excluded either because of a long illness with an indefinite history, or because of the fact that the disease began gradually with no recognizable time of onset. In such cases the enlarged spleen was the first sign of the disease. In spite of the probable errors, in view of the number of patients reported, it might be expected that if there was a seasonal variation in the incidence of the disease it would be reflected in the general trend of estimated months of onset; that is, provided there was not too great a variation in the incubation period. This has been estimated as ranging from two to 16 weeks. In this case a drop in the incidence of the disease would be expected four months after the suspected vector had ceased to be prevalent. This seemed to be borne out by the observations of Yuan et al.,<sup>20</sup> which will be mentioned shortly. However, our record revealed a fair degree of uniformity for all the months of the year. This was even more obvious if a leeway of a month, more or less, was allowed in either direction. This observation would not seem to support the theory of the sandfly as a vector, because those species in which flagellates develop become rare in July and August and practically extinct in September. If this theory is correct a drop in the incidence of onset would be expected some four months after August, as was discovered by Yuan.

In 1939 Yuan, Chu and Lee<sup>20</sup> reported a series of 36 infants with kala azar in the first year of life as seen in the Peiping Union Medical College

\* From a personal message from Dr. T. Yates, formerly of Hwaiyuan, Anhwei.

These were studied with reference to the estimated month of onset of the first symptoms as related to the month of birth. They found that allowing for a variable incubation period, in most cases the infection began in early summer, May 15 to July 15. This corresponded to the prevalence of *Phlebotomus chinensis*, the only sandfly so far known in China which can carry flagellates in its intestinal tract in the absence of gross blood, and also have them in its mouth parts. These infants had no chance of previous infection. Yuan emphasized that these data are more significant in infants than those on adults which are more variable and less reliable.

### EPIDEMIOLOGY

Although it has been known for a long time that kala azar is a communicable disease, it is only recently that proof of how it is transmitted has been obtained. A complete review of the work done on this problem would be impossible, so only a few of its high lights will be presented. Adler and Theodor<sup>21</sup> demonstrated the infection in dogs and in *Phlebotomus perniciosus* in the Mediterranean region. The work of Shortt and others in India from 1926 to 1932 has contributed a firm foundation to the present knowledge of sandfly dissemination and hamster inoculation. An interesting record of much of the research work on the epidemiology of kala azar is given in outline form by Forkner and Zia,<sup>22</sup> bringing it up to 1934. We shall review the work done on the problem in China in the Peiping Union Medical College, and only a few references will be made concerning other investigations.

Research on the epidemiology is hinged around two theories: the indirect and direct methods of transmission. The former is the one which has generally been favored by most investigators. In India, Shortt and others have developed the theory of a person to person spread through the sandfly as vector, whereas in the Mediterranean countries Adler with others has supported the theory of a canine host supplying sandflies with parasites, with subsequent infection of man by the infected flies. It is this theory which is now being studied in China. Chinese hamsters which are more susceptible than man are used in the experiments.

### THEORY FOR THE INDIRECT TRANSMISSION OF KALA AZAR

Sandflies were first suspected of being a possible vector by Pressat in 1905. Since that time flagellates have been found in bedbugs, fleas, lice and mosquitoes,<sup>22</sup> but as the parasites soon die out these have not been considered seriously as possible vectors.

Although canine leishmaniasis was recognized over a decade ago in the Mediterranean region by Adler, it was not found in China until 1934.<sup>23</sup> Lee<sup>24</sup> three years later found two dogs similarly infected. One of these was in a household where a child had kala azar. Only a few cases of canine leishmaniasis have been found in India in spite of the prevalence of human infection. (The disease in the dog is easily identified by the skin lesions which first appear around the eyes and at the base of the ears. They consist of the following signs in sequence of development: seborrhea, scaling, depillation, thickening, nodule formation and ulceration.<sup>25</sup>)

The work of Napier<sup>26</sup> showed that *Phlebotomus argentipes* was present only in kala azar endemic areas and that the prevalence of the disease corresponded with the sandfly incidence curve, allowing for a three to four month incubation period. In 1938 Wu and Sung<sup>27</sup> reviewed the work of previous investigators which showed that (1) Leishman-Donovan bodies undergo development in *Phlebotomus argentipes*, and that these are able to infect hamsters by their bite (Shortt et al., 1926 and 1931, and Napier, 1933); (2) *Phlebotomus chinensis* became infected from hamsters with kala azar (Young and Hertig, 1926); and (3) in 1935 flagellates were found in 5 per cent of the sandflies which had fed on patients. Wu and Sung allowed erect haired sandflies (*P. chinensis* and *sergenti*) to feed on patients and hamsters with kala azar. More flagellates were found in those flies which had fed on hamsters, probably because more parasites were available in the skin. Also more flagellates were found in *P. chinensis*, possibly because of a more suitable pH in the gut. They concluded that in this fly there was a tendency to a forward extension into the proventriculus, flagellates remaining motile four to six days after feeding. Feng and Chung<sup>28, 29</sup> in 1939 corroborated these findings after observing sandflies (*P. sergenti* and *chinensis*) artificially infected from four diseased dogs. Therefore *P. chinensis* was found to be the better host as it could maintain an active infestation. Chung et al.<sup>30</sup> examined 587 apparently normal dogs and found leishmaniasis in the viscera of 1.4 per cent.

Hoeppli<sup>31</sup> in a review of the epidemiology mentioned that direct transmission was not an important consideration as the parasites died in the feces, urine and oral (or nasal) secretions when dry. He referred to the investigation of Chung and Wang<sup>32</sup> who showed that intraperitoneally infected hamsters cured of *Leishmania donovani* with neostibosan were immune from inoculations of *L. canis*. From this it was inferred that the two diseases might be identical, and that *P. chinensis* passed it from dog to man. In 1940 Chung,<sup>33</sup> continuing the study of the relationship between human and canine kala azar and between *L. donovani* and *L. canis*, noted that dogs might constantly be a source of infection and that all infected dogs had passed through at least two sandfly seasons. Chung and Feng<sup>34</sup> found visceral lesions in a hamster which had received an intraperitoneal injection of the saline suspension of parasites from *P. chinensis* which had fed on an infected dog.

Until recently (in China) only these two erect haired types of *Phlebotomus* (*P. chinensis* and *sergenti*) have been found capable of carrying parasites. However in 1938 Yao and Wu<sup>35</sup> found a new form of erect haired fly and suggested the name *P. kiangsuensis* as it was found in Chingchiang, Ku. Later the same observers<sup>36</sup> reported the presence of *P. barraudi*, another erect haired type, in Yunnan. Later these may also be shown to be carriers of flagellates.

What may prove to be the last link in the chain of evidence incriminating the sandfly as the vector of kala azar was forged by Swanmath, Shortt and Anderson in 1942.<sup>37</sup> These investigators were able to infect man through the bites of *P. argentipes* which had fed on a patient with leishmaniasis. They attributed their success to the fact that after infection the flies were fed on raisin juice rather than blood, which was the food used by other investigators who had failed in demonstrating this vital step. No reason can yet be offered why raisin juice seemed the cause of their success. Although this may not be the final proof of the epidemiology of the disease, it would seem that if this work is supported by others it is indeed the beginning of the final chapter.

#### THEORY FOR THE DIRECT TRANSMISSION OF KALA AZAR

This rests on the presumptive evidence that Leishman-Donovan bodies which were obtained from tonsillar and nasal secretions, caused an infection when injected intraperitoneally into hamsters.<sup>22</sup> From this it is concluded that the disease can be

conveyed by Leishman-Donovan bodies as well as by the flagellate form of the parasite. Hamster infection was similarly brought about by the injection of urine and prostatic fluid of patients with kala azar.<sup>88</sup>

### SUMMARY

The evidence supporting the indirect transmission theory rests primarily upon: (1) the finding of the flagellate form in the sandfly; (2) the susceptibility of the sandfly to infection by feeding on patients, hamsters and dogs with kala azar; (3) the ability of the sandfly to infect hamsters; (4) the presence of parasites in *P. chinensis* after the disappearance of blood from the gut, and their forward extension into the proboscis; and (5) the transmission of the disease to healthy adults through the bites of sandflies which had fed on a patient with kala azar. It is supported secondarily by the apparent similarity between the canine and human infection, as shown by similar immune reactions to both types in hamsters.

Direct transmission would seem a simpler solution, but the argument against it lies in the early death of the parasite when dried. Therefore if this is the only means of spread, all cases must have been exposed directly to an infected individual, or to their moist secretions.

### SEROLOGY

Chung and Lu<sup>39</sup> carried out complement fixation reactions with the serum of patients, dogs and rabbits with kala azar against antigens of *L. canis* and *L. donovani*. Practically identical reactions occurred in each instance. They suggest that dissimilar results in previous reports are due to faulty technic, or a difference in antigen preparation.

### PATHOLOGY

Assuming the sandfly is the vector, the first stage of the disease is the implantation of the flagellates into the skin. From here they are carried to the lymph node of that particular region, where they multiply as Leishman-Donovan bodies throughout the incubation period. Finally the lymph node is no longer able to contain them, and they break through their local confines, entering the blood stream. (No doubt it is this incident which is the cause of primary fever and chill.) The circulating parasites are removed by the reticulo-endothelial cells wherein they multiply until the cell is ruptured. Mononuclears, clasmotocytes and leukocytes also serve in removing the parasites from the blood stream.

The reaction of the cells to this process determines the pathological picture. In the spleen there is a distention of interlobar capillaries, a proliferation of parasitized cells and an increase of connective tissue. Hu<sup>40</sup> described a decrease in the number of parasites accompanying treatment or complications. He also mentioned that there is an enlargement of the liver with parasites in the Kupffer and hepatic cells resulting in atrophy and cir-

the umbilicus as compared with 49 per cent of those with a six month illness. Therefore in patients with a disease of over six months' duration there was an even higher percentage reaching below the umbilicus, and a still further increase after 18 months. From these findings it may be inferred that the rate of enlargement is greatest during the first six to nine months of illness.

Muir<sup>43</sup> and others have stated that there is a characteristic rise of temperature twice a day. In a series of 49 uncomplicated in-patients there was only one who showed this curve. Most of the patients had a malarial type of fever with a daily rise and fall, and a smaller number maintained a continuous low grade fever until it fell with treatment. Children showed less fever than adults, even when their disease was of longer duration.



FIG. 2. A child with kala azar having situs transversus.

In this same group of in-patients undergoing treatment the elevation of temperature averaged less than  $100.5^{\circ}$  F. in 90 per cent of the cases. There were occasional peaks of fever far above the average, but these were unusual. A comparison of the pulse rate with the fever revealed a much more rapid pulse than would be expected for the temperature. This may be due to the cachectic condition of most in-patients, those less ill being treated in the clinic. Sixty-six per cent of the 49 uncomplicated in-patients undergoing treatment maintained a continuously normal temperature after the eleventh day, only four of these being afebrile at the outset. All groups of patients, regardless of age and duration of the disease, responded similarly to treatment, although those over 10 years of age with an illness under six months became free of fever sooner than others.

## LABORATORY FINDINGS

*Indirect Evidence*

1. *Anemia.* This was frequently striking and usually seemed to be of the simple secondary type with no demonstrable variations from the normal erythrocyte morphology. However, on frequent occasions, especially in more advanced anemias, there was definite hypochromia. The erythrocyte count was reduced in proportion to the hemoglobin. Unfortunately insufficient records were obtained after treatment for comparison, yet there was no question but that the anemia began to improve soon after commencing treatment, even without supportive iron therapy.

TABLE II  
Hemoglobin \*

Hgb. %	10-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80
No. cases	1	4	5	11	13	36	16	46	19	20	22	36	5	4
% cases	.42	1.70	2.1	4.62	5.46	15.1	6.75	19.3	8.0	8.4	9.24	15.1	2.1	1.7

\* Estimations performed on a standardized Sahli instrument.

This table shows that 55 per cent of the patients had a hemoglobin reading of 50 per cent, or under. Studying the cases individually, there was a tendency for a greater degree of anemia in patients with a disease of longer duration, especially in children.

2. *Leukocyte counts* are reported in table 3, and will be discussed thereafter. An increase in the white cell count was one of the first signs of successful treatment, occurring even during treatment. Complete remission was secondary to an increase in the number of leukocytes, as illustrated by apparently spontaneous cures which follow a leukocytosis from complications, such as noma.

TABLE III  
Leukocyte Counts

	1500	2000	2500	3000	3500	4000	4500	5000	5500	6000	over 6500
No. cases	24	28	45	37	22	31	24	19	8	8	33
% cases	8.6	10.13	16.12	13.25	7.87	11.1	8.5	6.9	2.87	2.87	11.79

This table shows that over 50 per cent of the patients had counts below 4,000 per cu. mm. Contrary to our expectations younger patients revealed a better leukocytic response, even with a long standing illness, than did the older patients, many of whom had been ill for less than six months. Patients over 10 years of age with a disease of over six months' duration quite definitely showed the poorest response, 55 per cent having counts below 3500



per cu. mm. This may account in part for the higher incidence of complications in older patients with a protracted illness.

3. *Differential counts.* Unfortunately these were not carried out routinely on uncomplicated cases, but there is no question as to the lowering of the polymorphonuclear percentage and an increase in lymphocytes.

4. *Platelet counts and bleeding times.* A series of these examinations carried out on two small groups, with and without epistaxis, failed to show any definite relationship of this symptom to thrombocytopenia or a prolonged bleeding time.

5. *Water test (globulin precipitation, or hemolytic test).* This is positive because of an increase in serum globulin which is also present in Banti's syndrome, schistosomiasis, chronic malaria and occasionally typhoid fever.<sup>44</sup> Positive reactions are graded from 1 to 4 plus, and in nearly all cases the reaction is strongly positive. This test remains positive for a number of months after remission following treatment.

In the presence of a positive water test together with leukopenia and splenomegaly, we consider the diagnosis certain and give treatment even if Leishman-Donovan bodies are not found in the marrow or liver smears.

Other indirect tests for kala azar are the formol-gel and antimony reactions which will not be discussed as we have not used them.

#### *Direct Evidence, or Demonstration of the Leishman-Donovan Bodies*

##### 1. In the blood.

a. By smear. This was relied upon before liver and sternal punctures were used. It is possible, if not probable, that these would frequently be positive if smears could be made during the first febrile seizures when the parasites may be in the blood stream. Wang<sup>45</sup> found blood smears positive in 39 per cent of his cases. The smear was made so that it was thick at the end where leukocytes and parasites accumulated.

b. By blood culture. This method is described in Cecil's Medicine using blood diluted with N.N.N. medium. It is incubated 6 to 18 days at 22° C. to prevent the growth of other organisms, which even then is frequent. But it is usually positive, the flagellate form appearing.

2. In the lymph nodes parasites have been demonstrated either in a biopsy section, or in the material removed by a trochar.

3. In the spleen. Splenic taps have long been employed routinely and are usually positive. Muir<sup>43</sup> described this procedure, giving a careful account of his technic in 1,000 examinations without a mishap, employing carbolic acid as a skin anesthetic. However, owing to splenic friability and danger of hemorrhage, this method of diagnosis has been largely abandoned. We used it only twice in as many years in cases presenting unusual diagnostic difficulties.

4. In the liver. In spite of a similar danger of hemorrhage from tearing, especially in crying children, this method is still used routinely by many

examiners. Although only a very small amount of tissue is removed, a fine bore hypodermic needle being used, parasites are almost invariably present and easily found.

5. In the bone marrow. Aspiration of tibial marrow was first carried out, but because of the thickness of the cortex this site was impractical. Examination of the bone marrow for Leishman-Donovan bodies did not become popular until the introduction of sternal punctures. Our use of this method was initiated by an article by Chung<sup>46</sup> in 1938. We have employed the usual technic in making sternal punctures. A fine caliber spinal puncture needle which had been shortened to approximately one inch in length was used. A few drops of marrow were withdrawn by a small syringe. The marrow was spread on a clean slide and was stained by Wright's or Leishman's stain. A longer time is necessary than for blood cells, as the parasites absorb the stain more slowly. (This method has also proved valuable in the diagnosis of malaria in difficult cases.)

In case the sternal smears were negative, then leukocyte counts, hemoglobin determinations and water tests were done. If these were characteristic of kala azar and if the spleen was enlarged, there was ample indication for treatment. On the other hand, if these were all negative but if the spleen was enlarged, a liver tap was done. In case this also was negative, the patient was told to return in one month for a further examination. However such instances were rare. At times a second sternal puncture was carried out instead of a liver tap.

TABLE IV  
Sternal Punctures and Liver Taps

Sternal Puncture	Positive	Negative	Total	Liver Tap	Positive	Negative	Total
First	452(81%)	105(19%)	557	Original	2		2
Second	3(38%)	5(62%)	8	After sternal puncture	24(53%)	21(47%)	45

6. Leishman-Donovan bodies are also found in the tonsil and nasal smears,<sup>22</sup> and also in the feces. Owing to the difficulty of finding them, these examinations are of only experimental interest.

#### DIFFERENTIAL DIAGNOSIS

When the parasites are found there is no question as to the diagnosis. When they are not identified and other supportive findings are absent, which is infrequent, the question of diagnosis arises. Chronic malaria, Banti's syndrome and schistosomiasis (prevalent in the Yangtze valley) should be considered. More acute infections, such as malaria, typhoid fever, Malta and relapsing fevers, may also be simulated by kala azar.

## COMPLICATIONS

When a remission followed treatment the patient rarely had any subsequent illness. Therefore other diseases were coincident with the kala azar itself. Complications were relatively more common in adults than in children. Most patients with complications had a resistance lowered by a protracted disease, and also had an especially low leukocyte count with which to combat the invading organisms. When children were attacked, they seemed better fitted to resist the added disease, even when quite ill from the kala azar. Naturally most complications occurred in children as their number was so much greater.

The following table includes the most frequent complications and causes of death observed in the 585 patients. As many patients had more than one complication, there was a greater number of these than the number of patients thus affected. Practically all new patients who were severely ill were admitted to the hospital. Out of the entire group there were 30 known deaths, a mortality rate of 5.1 per cent. Four of these were in clinic patients, three of whom had no complications.

TABLE V  
Complications

Diseases	Surviving		Deaths
	Clinic	Admissions	
Pneumonia (all forms).....	3	12	9
Acute bronchitis.....	15	5	
Acute pharyngitis.....	5	1	1
Gangrenous stomatitis (noma).....	5	7	3
Fusospirochetosis.....		2	3
Bacillary dysentery.....	15	5	1
Amebic dysentery.....		1	
Diarrhea (undetermined cause).....	12	2	
Ascites.....	3	7	
Acute (glom.) nephritis.....		6	1
Edema.....	4		
Otitis media.....	4	1	
Abscess (post injection).....	4	2	

Other complications were lung abscess, acute pleurisy, pulmonary tuberculosis, empyema, acute laryngitis, diphtheria, bacterial endocarditis, poliomyelitis, gonorrheal conjunctivitis, acute cervical adenitis, synovitis, parotitis, chickenpox, idiopathic purpura, streptococcic and staphylococcic bacteremia and erysipelas. Deaths also occurred with pulmonary tuberculosis, empyema, pleural effusion, Ludwig's angina, bacterial endocarditis, intestinal hemorrhage from typhoid fever and advanced anemia.

Special mention should be made regarding the complication of noma. This dreaded condition has been the cause of death in many patients, whereas in others it has apparently resulted in a remission (cure). In our series it

occurred only in one patient over the age of 15, which corresponds with the observations of others. Infrequently older men are seen with noma scars and state that when young they had enlarged spleens which disappeared without treatment after the noma had healed. Clow<sup>19</sup> mentioned the frequency of bronchitis and dysentery in 100 cases, 14 of whom had noma with a death rate of 64 per cent. Fan and Scott<sup>17</sup> reported a 15 per cent mortality rate in 20 cases of kala azar with noma. Two of our three deaths in patients with noma occurred shortly after admission before treatment was started, and seemed to be due to a severe toxemia from the infection. In the third patient treatment had been completed and there was a rise in hemoglobin and leukocyte count before the patient succumbed to heart failure following bacterial endocarditis.

### RELAPSES AND IMMUNITY

Although each patient was told to return a month after treatment was concluded for an examination and sternal puncture, so few followed this advice that it does not seem worthwhile to make a detailed report of these cases. It is probably safe to say, however, that those patients who successfully completed treatment without any mishaps returned home to regain good health. Those who did return for reexaminations frequently still showed Leishman-Donovan bodies in their marrow. If the general condition was good, this finding was disregarded for the time and the patient was told to return in another month for a second smear. In such cases this was usually negative. (It has already been mentioned that the parasites disappear from the marrow more slowly than from the spleen and liver.) Therefore, although for diagnosis the finding of the parasites was of supreme importance and the other blood changes and symptoms were secondary, in determining relapses it was more important to check the leukocyte count, hemoglobin and general condition. Provided these were favorable, the continued presence of parasites did not indicate that the disease had not been treated satisfactorily. On the other hand, in cases which presented a continued leukopenia, cachexia and anemia after treatment, even if parasites were not found, a second course of treatment was seriously considered.

In this series there occurred six known relapses. Three of these appeared several months after treatment, and would therefore seem to be due to insufficient dosage. The other three had an apparently normal health period ranging from 6 to 24 months, during which time there was not only a remission of clinical symptoms, but also an absence of parasites in the marrow and liver smears. We may consider that such cases, in spite of a long remission period, are also probably relapses due to insufficient treatment, although there is some possibility of a reinfection.

*Immunity.* The work on this problem is still largely in an experimental stage and is bound up with the apparent equivalence of *L. canis* and *L. donovani*. Chung and Wang<sup>32</sup> cured five hamsters of *L. donovani* infection,

after which two of these were relatively and three completely immune to reinfection with *L. canis*, the controls having died. Chung<sup>39</sup> in cross complement fixation examinations found that antigens of *L. donovani* and *L. canis* gave equally strong positive complement fixations, supporting the theory that the two forms of leishmania are identical. Wang and Chung<sup>47</sup> treated 13 hamsters having kala azar with 20 grams of neostibosan per kilogram. (This is 400 times the dose used for man, which is about 50 mg. per kilo.) In this series they obtained only a 47 per cent cure after six months. Out of these, six became partially immune to a second infection, and four completely so. The excretion of antimony may be faster in hamsters than in man, and this may account for the need of larger doses, and a lower rate of cure.

### PROPHYLAXIS

This is based on what is known of the epidemiology of the disease and would consist of the eradication of dogs with leishmaniasis, the removal of such conditions as would contribute to the breeding of sandflies, and the isolation of cases.

### COURSE AND PROGNOSIS

In China the course of the disease is long. After a variable period of normal activities the patients become weak, emaciated and anemic so that they are unable to work or play. Fever accentuates their anorexia and augments these symptoms. However, they remain ambulant until some complication supervenes and death ensues. Only three of our cases died of uncomplicated kala azar. Under treatment, if there are no complications, a remission follows in an almost unbelievably short time considering the length of illness in most patients. When treatment was first started, in some patients there was found an actual enlargement of the spleen or tenderness on palpation. It is an interesting question whether or not this is associated with the stage of proliferation described by Wang<sup>42</sup> in hamsters undergoing treatment. In approximately one-third of the patients there occurred a rise of temperature after the first or second injection. This was brief and may have been due to the drug. After the fall in temperature there followed an increase in leukocytes and hemoglobin. Clow<sup>19</sup> reported an average increase of 2,510 leukocytes and 4.5 per cent hemoglobin during treatment in 100 cases. After discharge the patients regained strength and weight, the spleens gradually became smaller and within a few months children were once more able to play and adults return to their occupations.

### TREATMENT

It has been only a few decades since multivalent antimony compounds became available. Thereupon kala azar could be adequately treated with a rate of cure of 90 per cent or more, and with little fear of drug reactions. Prior to this, treatment was risky and unsatisfactory.

*To produce leukocytosis.* With the discovery of leukopenia it was believed that a remission would follow an increase in the white cell count. In order to accomplish this a number of methods have been employed. In Syria a seton was introduced through the skin over the spleen by which means a permanent sinus was kept draining.<sup>43</sup> In China a large number of patients come in with a plaster of local medicine applied over the enlarged spleen. Whether or not there is any effect on the leukocytes cannot be stated.

Physicians have also tried to produce leukocytosis by injections of sodium nucleate, staphylococcus vaccine, or by camphor, creosote and turpentine in olive oil. Hu<sup>48</sup> studied the influence of parenteral injections of dead bacteria and foreign proteins on experimental kala azar infection in hamsters. His experiments showed a larger spleen in these hamsters than in a series of untreated controls, because of a reticulo-endothelial proliferation and cell infiltration, but with fewer parasites.

*To eradicate the parasites:* Tartar emetic was probably the first antimony compound used in the treatment of kala azar. It was given in a 1 or 2 per cent solution intravenously, starting with doses of 0.5 increased to 3 c.c. Three injections were given weekly over a period of nearly four months, until a total dosage of 2 to 4 gm. had been administered. Many reactions and complications occurred, especially broncho-pneumonia. Similar doses of the heavy salt of sodium antimonyl tartrate were used by Muir.<sup>43</sup> This drug was less toxic, and produced remission of fever in a month.

Urea stibamine has been used chiefly in India, with no ill effects, but it seems that little of the compound has been available in China, although one observer<sup>49</sup> gave a short report on its effect. He stated that it was more potent and more toxic than neostibosan, and was not so well standardized as the antimony content varied from 20 to 43 per cent.

Neostam is a pentavalent antimony compound which was used extensively in many if not in most of the largest kala azar clinics in China. Its dose is based on body weight, being approximately one gram for each 33 pounds. Although many who used it reported that reactions were unusual, we did not find its use in the clinic feasible because of severe vomiting and at times diarrhea. Clow<sup>19</sup> also mentioned vomiting as a distressing reaction. Bed patients rarely react to it, but as most of our patients were treated in the clinic we gave it to a smaller portion of the entire series. There were several hundred of these, and they responded as satisfactorily as did the others who received neostibosan. However, many of this group suffered an accentuation of their bronchitis under neostam, which rarely occurred with neostibosan.

Neostibosan (diethylamine p-aminophenyl stibinate) containing 42 per cent antimony was the drug which we used most regularly as reactions were mild or absent and as it was uniformly effective. The dose was similar to that of neostam, although with children under 33 pounds a full gram was given, and three grams cured adults weighing up to 110 pounds. Usually the largest dose employed was 3.5 grams, although for a period we occasionally gave as much as 4 grams. This was still a smaller dose than some others have used, but our results would seem to justify it.

Clinic patients received three injections a week on alternate days with individual injections varying from one-fifteenth of the total dose at the out-

set, to one-eighth toward the last of the course. Children usually finished the treatment in nine injections, and adults in eleven. In-patients received daily injections as they could be kept in bed and their condition observed more accurately. These completed their treatment in 13 to 16 days as somewhat smaller doses were given daily than when administered every other day.

The dangers of a routine system of dosage based on weight are many, as individual variations require readjustments in many instances. We tried to accommodate the dose to such variations, but no doubt sometimes failed. Occasionally a larger amount of antimony is needed, especially in those who are more severely ill, but not necessarily in those with a longer history. Practically all injections were given intravenously in 0.5 per cent solution because when the drug is given intramuscularly sterile abscesses may occur.

Antimony is definitely contraindicated in the presence of jaundice, hepatitis, nephritis, or pneumonia. Although in the presence of bronchitis treatment was given, the patient was admitted as pneumonia might ensue. If we had withheld treatment in all cases of bronchitis, many would have been left untreated. We also gave the drug in the presence of ascites without any untoward reactions.

Whether or not it is advisable to withhold treatment in the presence of noma seems to be an undecided question. Some authorities advise this, and await the limitation of the process. Chu<sup>49</sup> and Fan and Scott<sup>17</sup> continued routine treatment not only without misadventure, but even with good results. This is the procedure we followed, and neither did we meet with any adverse reactions, but rather found that these patients responded well with an early limitation of the necrotic process.

In conclusion it must be admitted that so little is known of the antimony concentrations necessary to be parasiticial, of its storage in the body and of its elimination rate that treatment is based on purely empirical grounds. It is hoped that in the future there will be introduced suitable analytical methods which will answer these questions.

### CONCLUSIONS

1. Kala azar is endemic throughout north China with an especially high incidence from southern Shantung to the Yangtze River. The disease seems to follow in the wake of famine, flood, drought and war.

2. It is most common below the age of 15, although this series contained an unusually large number of patients from 15 to 40 years of age. Most of the patients are from the farmer or coolie class living in small villages.

3. A study of the epidemiology points to the sandfly as vector, and the dog as reservoir host for the parasites. This is borne out by (a) the ability of *Phlebotomus chinensis* to receive and retain the parasites even in the absence of blood, (b) the growth of flagellates in the intestine of the fly and their forward extension into the proboscis, (c) the apparent identical nature of *Leishmania canis* and *donovani* as revealed by similar complement fixation

reactions, and (d) direct transmission of the disease to man through the bite of infected flies.

4. The most important physical signs are an enlarged spleen usually reaching to the umbilicus within 12 months, a low grade fever with tachycardia, an anemia most pronounced in children with a longer illness, and a leukopenia which is more marked in the older and more chronic cases. All uncomplicated cases remained ambulatory.

5. Sternal marrow smears were positive in 81 per cent of 557 examinations, and constituted the most valuable means of diagnosis.

6. Complications were more frequent in older patients with a more protracted history. The most common of these were pneumonia, amebic and bacillary dysentery, bronchitis and noma.

7. There were 30 known deaths in 585 patients, a mortality rate of 5.1 per cent. Only three of these succumbed to kala azar alone, the remaining having complications, the most frequent of which was pneumonia.

8. Six relapses were known to have occurred, three within a few months and three after a period of normal health and negative laboratory findings extending from 6 to 24 months.

9. Prophylaxis should consist of eradication of sandfly breeding places, removal of infected dogs and segregation of patients.

10. The course of the disease is chronic. Untreated cases gradually lose weight and strength until their debilitated condition makes them subject to some complication which is usually the cause of death. Kala azar responds readily to antimony treatment even in patients with a chronic infection.

11. Our treatment has consisted in the use of pentavalent antimony compounds (neostibosan and neostam), giving approximately one gram per 33 pounds of body weight in 9 to 16 intravenous injections of a 0.5 per cent solution. Very few reactions occurred with neostibosan except a brief fever at the outset of treatment. Gastrointestinal upsets were common in clinic patients receiving neostam, although these were rare in in-patients. After treatment the parasites disappear more slowly from the bone marrow than from the liver and spleen. Antimony is contraindicated in the presence of jaundice, hepatitis, pneumonia, or acute nephritis.

12. Before a sound rationale of treatment can be laid down, more information must be obtained concerning the least concentration of the drug which is parasiticial, its storage in the tissues and rate of elimination.

#### BIBLIOGRAPHY

1. COLTMAN, S.: Chinan Dispensary Reports, 1887-88 (not obtainable).
2. YOUNG, C. W.: Kala azar in China, *Chinese Med. Jr.*, 1923, xxxvii, 10.
3. ASPLAND, W. H. G.: (report), *Chinese Med. Jr.*, 1911, xxv, 212.
4. JEFFRYS, W. H., and MAXWELL, J. P.: *Diseases of China*, 1929, Shanghai.
5. COCHRAN, S.: Kala azar in Hwaiyuan, *Chinese Med. Jr.*, 1911, xxv, 272-273.
6. COCHRAN, S.: The superficial lymph nodes as a source of *Leishmania* for diagnosis in cases of kala azar, *Jr. Trop. Med.*, 1912, xi, 179.
7. REED, A. C.: Report North China, *Jr. Am. Med. Assoc.*, 1914, lxiii, 1572.



8. WYLIE, J. H.: Kala azar in north China, Chinese Med. Jr., 1929, xxxiv, N. 5.
9. Weihsien Hospital Report, Chinese Med. Jr., 1924, xxxviii, N. 4.
10. Weihsien Hospital Report, Chinese Med. Jr., 1925, xxxix, N. 9.
11. KING, G. E.: Kansu and its diseases, Chinese Med. Jr., 1925, xxxix, 19.
- 12 and 13. TAYLOR, H. W. Y.: Kala azar in Mukden, Chinese Med. Jr., 1931, xlv, N's. 1 and 2.
14. MORRIS, H. H.: Kala azar from S. Kiangsu, Chinese Med. Jr., 1931, xlv, 1180.
15. STURTON, S. D.: Report from Chekiang, Chinese Med. Jr., 1931, xlv, 146.
16. Report from Kiangsi, Chinese Med. Jr., 1933, xlvii, 12.
17. FAN, P. L., and SCOTT, A. V.: A study of noma complicating kala azar in children, Chinese Med. Jr., 1934, xlviii, 1046.
18. DU, S. D., and BEST, A. E.: Kala azar in W. China, Chinese Med. Jr., 1936, 1, 273.
19. CLOW, J. M.: Shansi province as an endemic focus of kala azar, Chinese Med. Jr., 1941, lix, 150.
20. YUAN, I. C., CHU, F. T., and LEE, C. U.: The seasonal incidence of kala azar in infants and its significance in relation to the transmission problem of the disease, Chinese Med. Jr., 1939, lvi, 241.
21. ADLER, S., and THEODOR, O.: Skin infection in canine visceral leishmaniasis, Brit. Med. Jr., 1931, ii, 1179. Investigations in Mediterranean kala azar; further observations in canine visceral leishmaniasis, Proc. Roy. Soc., London, sb., 1935, 116, 494-504.
22. FORKNER, C. E., and ZIA, L. S.: An outline of the development of theories for transmission of leishmaniasis, Trans. of 9th Cong. of Far East Assoc. Trop. Med., 1934, i, 633.
23. ANDREWS, M. N.: A case of canine kala azar occurring in China, Trans. 9th Cong. of Far East Assoc. Trop. Med., 1934, i, 679.
24. LEE, C. U.: Canine leishmaniasis in Peiping, Chinese Med. Jr., 1937, 1, 951.
25. CHUNG, H. L., HOEPLI, R., and FENG, L. C.: Histopathological observations in 12 cases of canine leishmaniasis in Peiping, Chinese Med. Jr., Supp. iii, 1940, 212.
26. NAPIER, L. E.: The transmission of kala azar in India, 9th Cong. of Far East Assoc. Trop. Med., 1934, i, 657.
27. WU, C. C., and SUNG, C. J.: Kala azar transmission, Chinese Med. Jr., Supp. ii, 1933, 579.
28. FENG, L. C., and CHUNG, H. L.: The development of leishmaniasis in Chinese sandflies fed on dogs with canine leishmaniasis, Chinese Med. Jr., 1939, lvi, 35.
29. CHUNG, H. L., and FENG, L. C.: Natural infection of *Phlebotomus chinensis* with leishmania flagellates, Chinese Med. Jr., 1939, lvi, 47.
30. CHUNG, H. L., et al.: A report on 587 normal dogs in Peiping for leishmania infection, Chinese Med. Jr., 1939, lvi, 354.
31. HOEPLI, R.: The epidemiology of kala azar in China, Chinese Med. Jr., 1940, lvii, 364.
32. CHUNG, H. L., and WANG, C. W.: The immunity of infection with *Leishmania canis* to hamsters recently cured of *Leishmania donovani* infection, Chinese Med. Jr., 1939, lvi, 519.
33. CHUNG, H. L.: On the relationship between canine and human kala azar in Peiping, and identity of *Leishmania canis* and *Leishmania donovani*, Chinese Med. Jr., 1940, lvii, 501.
34. CHUNG, H. L., and FENG, L. C.: Further observations on natural infection of *Phlebotomus chinensis* in Peiping with leishmania flagellates, Chinese Med. Jr., 1941, lix, 540.
35. YAO, Y. T., and WU, C. C.: *Phlebotomus* in Tsingkiangpu, Chinese Med. Jr., Supp. ii, 1938, 527.
36. YAO, Y. T., and WU, C. C.: Notes on the Chinese species of genus *Phlebotomus*, etc., Chinese Med. Jr., 1941, lx, 79.
37. SWANMATH, C. S., SHORTT, H. E., and ANDERSON, L. A. P.: Transmission of Indian kala azar to man by the bites of *Phlebotomus argentipes*, Ann. 7. Brun., Indian Jr. Med. Research, 1942, xxx, 473.

38. TENG, C. T., and FORKNER, C. E.: The presence of Leishman-Donovan bodies in the urine and prostatic fluid of kala azar patients, Chinese Med. Jr., Supp. 1, 1936, 394.
39. CHUNG, H. L., and LU, L. D.: Cross complement fixation in kala azar, Chinese Med. Jr., 1941, lix, 301.
40. HU, C. H.: Pathological anatomy of kala azar with special references to certain hitherto less well recognized changes, Chinese Med. Jr., Supp. 1, 1936, 1.
41. PAI, H. C., and HU, C. H.: Absence of leucolysin in kala azar serum, Chinese Med. Jr., Supp. ii, 1938, 151.
42. WANG, C. W.: A histopathological study of the spleen of kala azar hamsters undergoing treatment with neostibosan, Chinese Med. Jr., Supp. iii, 1940, 564.
43. MUIR, E.: Kala azar, its diagnosis and treatment, 1918, Butterworth & Co., Calcutta.
44. LEE, C. U., and CHUNG, H. L.: A clinical study of the early manifestations of Chinese kala azar, Chinese Med. Jr., 1935, xlix, 1281.
45. WANG, C. W.: Examination of blood smears for *Leishmania donovani* in kala azar patients, Chinese Med. Jr., 1937, lii, 433.
46. CHUNG, H. L.: Sternal puncture technique and its clinical value, Chinese Med. Jr., 1938, liv, 397.
47. WANG, C. W., and CHUNG, H. L.: Further observations on neostibosan in the treatment of kala azar in Chinese hamsters, etc., Chinese Med. Jr., 1940, lviii, 601.
48. HU, C. H.: The influence of parenterally introduced killed bacteria and foreign proteins on experimental kala azar infection in hamsters, Chinese Med. Jr., Supp. iii, 1940, 179.
49. LEE, C. U., and CHU, C. F.: Relative value of urea stibamine and neostibosan in the treatment of kala azar, Chinese Med. Jr., 1935, xlix, 328.

# PERIARTERITIS NODOSA: OUR PRESENT KNOWLEDGE OF THE DISEASE\*

By MARSH MCCALL, Major, M.C., F.A.C.P., and JOHN WINTHROP PENNOCK, Major, M.C., F.A.C.P.,  
*White Sulphur Springs, West Virginia*

IN these days of chaos it may be stimulating to turn from subjects relating to war to a topic which dates from 1866, when Kussmaul and Maier<sup>1</sup> observed their first patient with arteritis. In their classical protocol a description of periarteritis nodosa is given in a patient who had enteritis, nephritis, and neuritis. In 1939 Harris, Lynch, and O'Hare<sup>2</sup> reviewed a total of 101 cases of periarteritis nodosa which had been reported in the English literature up to that date. From 1939 to 1942 we observed a group of seven male patients who came to autopsy with necrotizing lesions of the arteries and veins involving many organs, and this interest was further stimulated by our observation of five male patients who came to postmortem examination in a period of two months at Walter Reed General Hospital.† Since the beginning of the present war more than a score of soldiers have come to autopsy with this disease entity, the diagnosis being frequently made before death.‡ This fact emphasized our belief that the disease is not the rarity that it was once thought to be.

## ETIOLOGY

The etiology of this disease is unknown. Syphilis was long thought to be a causative factor, but this belief has not been borne out. This contention was largely based upon the observations of Chvostek and Weichselbaum,<sup>3</sup> whose patient had pupillary changes associated with encephalitis. In 1925 Gruber<sup>4</sup> reported his group, two of whom had positive serologic reactions. So far as we are able to determine from the literature, no observer has demonstrated a spirochete in a patient with necrotizing arteritis. It seems unlikely that syphilis plays any rôle whatsoever. A few clinicians have associated allergic manifestations with this disease. Harris and his associates have found allergy associated with 15 per cent of their patients. Rackemann and Greene<sup>5</sup> made a report at the Association of American Physicians, in 1939, relating the close association of asthma with periarteritis nodosa. Von Haun<sup>6</sup> and Harris<sup>7</sup> have been able to produce similar lesions in the arteries of rabbits by injecting the animals with bacterial products. There were

\* Read at the Columbus meeting of the American College of Physicians, May 14, 1943.

From the Medical and Pathological Services of the Ashford General Hospital, West Virginia.

† We gratefully acknowledge the assistance of Dr. Margaret Bevans of Bellevue Hospital, New York City, and Lieutenant William R. Randall of Walter Reed General Hospital, Washington, D. C., in the preparation of the pathological data.

‡ Personal Communication, Colonel James E. Ash, Army Medical Museum, Washington, D. C.

many points of similarity in our group suggesting a common infectious or toxic origin. The wide dissemination of the lesions, affecting the branches of the middle and small caliber vessels of almost every organ, has influenced us in our belief that they have a toxic etiology. The toxic origin of this morbid process has been thoroughly discussed by us.<sup>8</sup>

### CLINICAL MANIFESTATIONS

The clinical symptoms of our group were protean, because so many organs were involved. The onset was insidious, and often appeared subsequent to some obscure infection. The chief symptoms have been malaise, anorexia, asthenia, myalgia, and weight loss (figure 1). There was moderate weakness and cachexia. The temperature curve was either septic with

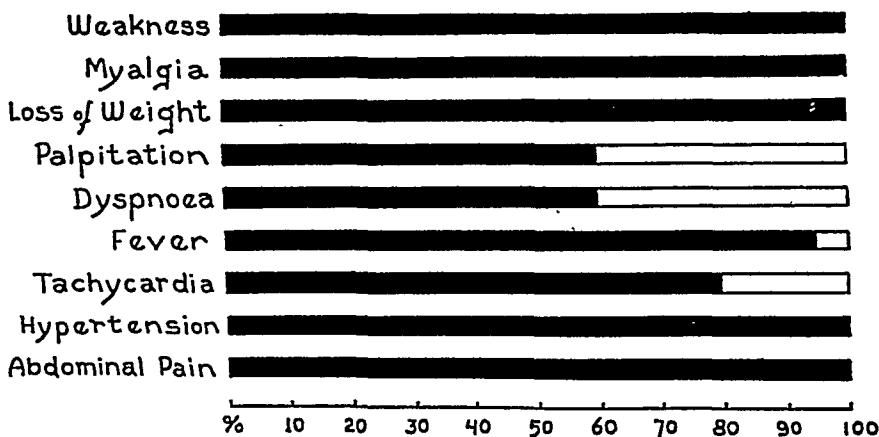


FIG. 1. Signs and symptoms of periarteritis nodosa (our series).

chills or was of the low, irregular variety. Complaints referable to the gastrointestinal tract were frequently encountered, but loss of appetite and vague abdominal distress were the most common problems. Ulceration of the mouth and diarrhea were less frequently noted. Evidence of cardiac involvement included precordial distress, palpitation, tachycardia, and congestive failure. Pericardial friction rub appeared late in the course of the disease on two occasions. The peripheral vessels were sclerosed far beyond the numerical age of the patient. There were signs of acute or chronic nephritis, with hyaline and granular casts, albuminuria and hypertension. Peripheral neuritis and paresthesias were sometimes seen early in the course of the disease. Obviously, all of the symptoms and signs cannot be enumerated, since necrotizing arteritis may mimic, at the same time, one or several diseases depending upon the organs affected (figure 2). For this reason we have scrutinized arterial changes in every young male with particular care. Pulsating subcutaneous nodules, thickened peripheral arteries, diminished or absent pulsation in a peripheral artery, gangrene, and Raynaud's phenomenon, associated with arterial obstruction, were suggestive and

helpful signs. The clinical picture in our patients varied strikingly, depending on the distribution and severity of the vascular lesions. In male patients with obscure, bizarre, and contrasting symptoms suggesting cachectic or infectious disease, the possibility of necrotizing arteritis was always considered.

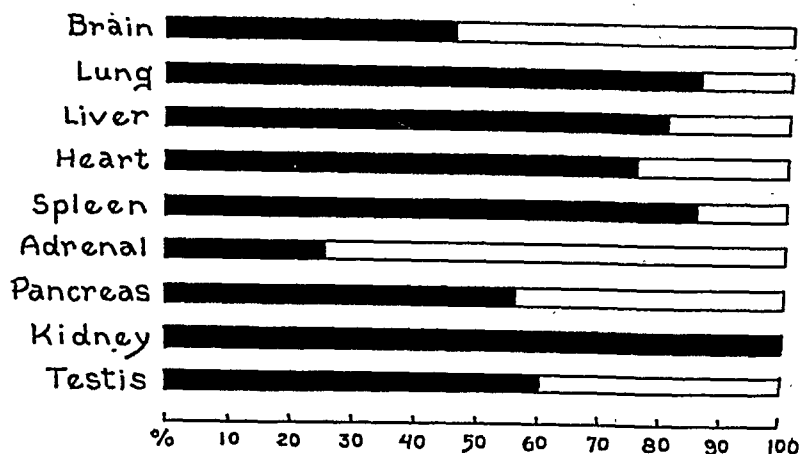


FIG. 2. Organs involved in periarteritis nodosa (our series).

### PATHOLOGICAL MANIFESTATIONS

1. *Pulmonary manifestations.* Ophuls<sup>9</sup> demonstrated extensive involvement of the pulmonary arteries and infiltration of the pulmonary parenchyma in his patients. In Gruber's series, four patients showed thromboses in the pulmonary vessels. In 1933 Herrmann<sup>10</sup> reported certain pulmonary changes in the roentgenogram of a patient with periarteritis. However, Herrmann's patient had suffered with severe asthma, whereas none of our patients had a history of any such allergic state. Our first patient had normal chest films until late in the course of the disease, when small conglomerate areas of increased density were noted at the bases, accompanied by diffuse infiltration, spreading out irregularly from the hilar zones (figure 3). As all of our later patients have died with bronchopneumonia, the roentgenograms taken before death revealed hilar and basal shadows of increased density, sometimes associated with areas suggesting cavitation and accompanied by a variable amount of pleural reaction. Pleural effusion was encountered in five instances, and empyema occurred just before death in a 32-year old soldier. Atelectasis was found bilaterally in several patients, but it was thought to be a terminal event associated with the pneumonic process. Large pleural effusions and empyema were rarely seen, but both bronchopneumonia and small effusions were regularly demonstrated. We believe that the pulmonary changes are frequently more extensive than roentgenograms and clinical observations disclose, and this was corroborated frequently at postmortem examination.

2. *Gastrointestinal manifestations.* All of our patients complained of vague abdominal distress, frequently associated with anorexia, but rarely

with vomiting. Terminally one soldier had two days of pernicious vomiting associated with right upper quadrant rigidity and tenderness. At autopsy the appendix showed early gangrene due to thrombosis of the appendiceal artery. Small petechial hemorrhages were occasionally found in the stomach and small bowel mucosa, and frequently there were arterial changes in the celiac and mesenteric vessels. The right superior gastric artery was completely thrombosed in one patient who was only 26 years of age. Chronic pancreatitis was noted in 50 per cent, as shown by increased fibrosis and small



FIG. 3. (A) Chest film taken six weeks before death shows no cardiac enlargement. A slight increase in the hilar shadows is noted. (B) Chest film taken of the same patient, one week prior to death, reveals slight enlargement of the heart shadow. There is a marked mottled density throughout both lungs, which is prominent at the lung root and extends well out into the periphery. These changes are often associated with extreme congestion of the pulmonary vessels.

areas of fibrinoid necrosis, which may account for the frequency of abdominal distress, even though diarrhea was encountered rarely. Several pancreatic specimens showed numerous vessels obliterated by thrombi. Three of the patients included in Gruber's study showed infarction with hemorrhage into the pancreas. Lamb<sup>11</sup> also mentioned infarction of the pancreas in his group.

3. *Hepatic manifestations.* Upper abdominal cramps were complained of frequently, but it was impossible to determine whether this was due to hepatic involvement. Clinical jaundice was present in three instances. Klotz<sup>12</sup> observed two patients with jaundice, whose histological examination showed areas of hepatic necrosis with hemorrhage, and thrombosis of the hepatic artery. In one of his patients liver necrosis was associated with

thrombosis of the cholecystic artery, and portal fibrosis similar to that seen in cirrhosis of the liver. Kountz<sup>13</sup> observed a patient showing icterus and peripheral neuritis, whose cholecystic artery and vein revealed thromboses. Pass<sup>14</sup> reported that periarteritis was the most frequent cause of infarction of the liver. Our specimens showed lesions in the hepatic vessels, but there was insufficient damage to produce cirrhosis.

4. *Endocrine manifestations.* Weakness was a complaint common to all, and it was profound in four patients. Whether this complaint had any direct relation to the adrenal changes cannot be said. However, the small adrenal arteries were occasionally surrounded by thick cuffs of monocytes, polymorphonuclear cells and plasma cells. Phlebitis and periphlebitis were sometimes noted, and, occasionally, complete occlusion of a vessel was found. Involvement of the testicular arteries and veins was noted in our first patient. We have found fibrinoid necrosis of the vessels four times. Just what disturbance occurred in the reproductive physiology was not determined. No lesions of the thyroid or pituitary vessels were found.

5. *Neurological manifestations.* Peripheral neuritis, associated with gangrene, was noted in two patients. Uncomplicated neuritis was evident in four others. Some complained of weakness and extreme fatigability, with pain in the calves of the legs after exercise. Occasionally, tenderness along the peroneal nerves could be elicited without any reflex changes. Twenty of Gruber's patients were said to have had peripheral neuritis, whereas only two of Spiegel's<sup>15</sup> group had peripheral involvement. The blood vessels of the cortex were occasionally infiltrated with inflammatory exudate with moderate thickening of their walls. Gross cerebral hemorrhage was never observed.

6. *Renal manifestations.* Moderate hypertension was a constant feature, being noted in every patient in this series. Moreover, albuminuria, with hyaline or granular casts, was common to all. Nitrogen retention was present terminally in 60 per cent, but the degree of nitrogen retention was not sufficient to produce uremia. Urea clearance was diminished in those patients showing nitrogen retention. That renal involvement is common in arteritis was noted by Arkin.<sup>16</sup> All of Spiegel's patients, who came to autopsy, had renal lesions. The lesions of malignant nephrosclerosis and those of chronic glomerulonephritis were occasionally encountered. These findings would suggest the vascular reaction in these kindred diseases might be caused by a similar toxin, or infectious agent.

7. *Cardiac manifestations.* Precordial distress and palpitation were frequent complaints. Heart consciousness and dyspnea were relatively common. The heart was enlarged terminally in all patients. In one patient the cardiac shadow widened just a few days before death. Sections taken through the endocardium have revealed inflammatory changes in three instances. No Aschoff bodies were found, but the valvular lesions appeared similar to those seen in acute rheumatism. This is in agreement with Fried-

berg and Gross,<sup>17</sup> who recorded four patients with the clinical picture of rheumatic fever, showing the valvular and myocardial lesions generally regarded as characteristic of rheumatic heart disease as well as valvular lesions characteristic of periarteritis nodosa. They believed that the arteritis in their group of patients was an expression of the rheumatic state. Both diseases probably have a common etiological factor, so it is conceivable that

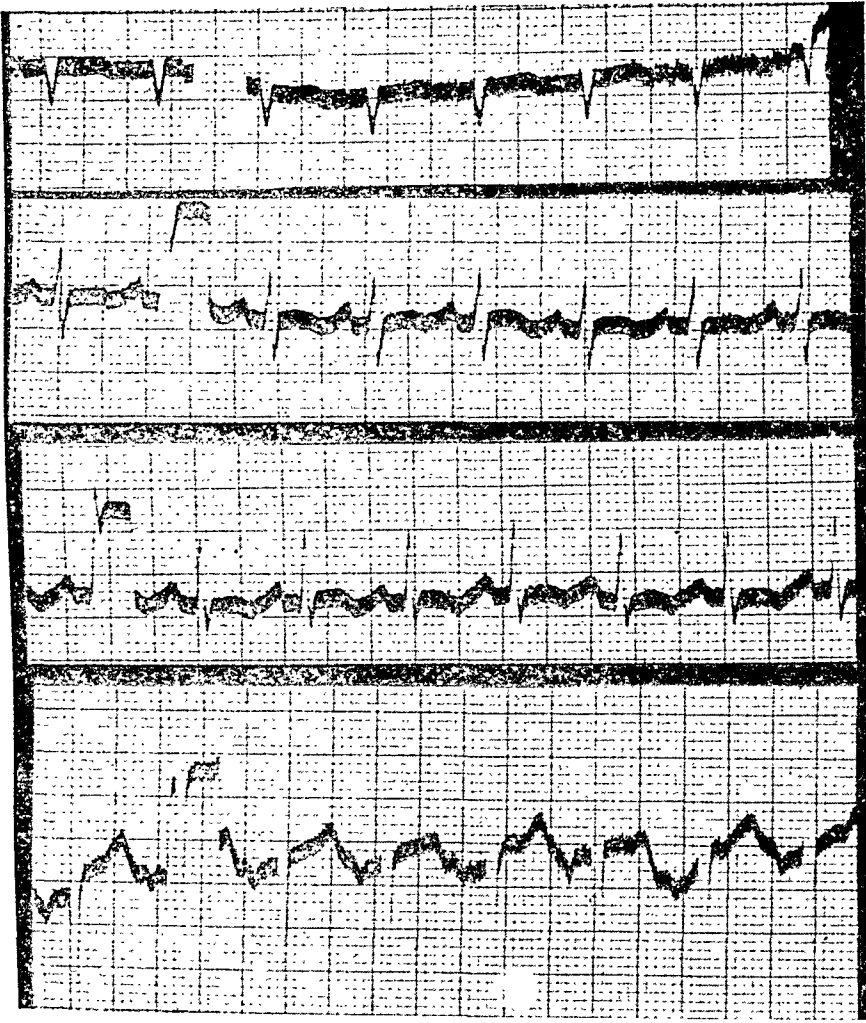


FIG. 4. Right axis deviation is indicative of increased pressure in the pulmonary circuit. T-wave changes indicate myocardial change.

these rheumatic lesions were due to necrotizing arteritis. It is a well known fact that verrucose vegetations are not specific of rheumatic carditis. Even Aschoff bodies may not be specific of the rheumatic state. Pericarditis was found on four occasions, and in one instance it was associated with dilatation of the ascending arch of the aorta. Branches of the coronary artery and vein were thrombosed in two of our group. Abnormal electrocardiograms were noted in the last weeks before death in all of our group (figure 4).



8. *Cutaneous manifestations.* Various skin lesions were found in 20 per cent of these patients. Among these were neurodermatitis, simple erythema, subcutaneous nodes and necrotic lesions.

9. *Joint manifestations.* Joint pain or myalgia was common to all. Actual joint swelling was observed in two soldiers, but there was no evidence of redness. Painful nodules were biopsied whenever they were found. These biopsies were never pathognomonic, but they revealed evidence of an inflammatory reaction about the small vessels.

10. *Laboratory manifestations.* From a laboratory standpoint the data obtained were those frequently noted in many chronic diseases. It was usual to find a moderate leukocytosis, but we have seen the leukocyte count elevated to 45,000. Eosinophilia was found in three patients, the highest being 7 per cent. Abnormal urinary excretion was common to all, manifested by albuminuria, cylindruria, and abnormal cellular content. Nitrogen retention was evident terminally in 60 per cent. *Staphylococcus albus* bacteremia was demonstrated in one soldier who had developed empyema due to the same organism.

## DISCUSSION

Many early observers stressed the periarteritic characteristics of this morbid process. It has been shown that the periarteritic lesions, occasionally striking on gross examination, are not the essential lesions of the malady. We have found that involvement of any or all grades of the blood vessels themselves might occur. In fact, not only arteries, but also the veins were involved (figure 5). From this standpoint the term periarteritis has been entirely too limited insofar as nomenclature is concerned. The disease, from a strictly anatomical point of view, may be divided into the macroscopic form which is recognizable from the obvious gross lesions, and the microscopic form which may be suspected indirectly by the multiplicity of lesions referable to the blood vessels.

Until recently many of the less evident pathological changes were not observed on gross examination, and unless serial sections have been made, the area of necrosis may well have been overlooked. The characteristic lesions of necrotizing arteritis usually appeared in the small and medium blood vessels, affecting as a rule the inner portion of the media and the intima. With the involvement of the intima one expected subendothelial proliferation, and with involvement of the media, elastica disruption and necrosis of the muscle occurred. The necrosis has been of a peculiar fibrinoid nature closely resembling that which has been observed in various manifestations of Libman-Sacks disease, malignant nephrosclerosis, and rheumatic fever. The kaleidoscopic manifestations of these diseases and the multiplicity of their lesions have been confusing. In patients with malignant nephrosclerosis one could very readily overlook the concomitant manifestations of the malady discussed in this paper. In patients with active rheu-

matic fever the presence of symptoms suggestive of glomerulonephritis has suggested to us a possible combination of necrotizing arteritis and rheumatic fever. In dermatomyositis one must differentiate this disease as an entity from dermatomyositis occurring in combination with periarteritis nodosa, and from dermatomyositis as it occurs in Libman-Sacks disease. A muscle biopsy without complete clinical data was not adequate in our ex-

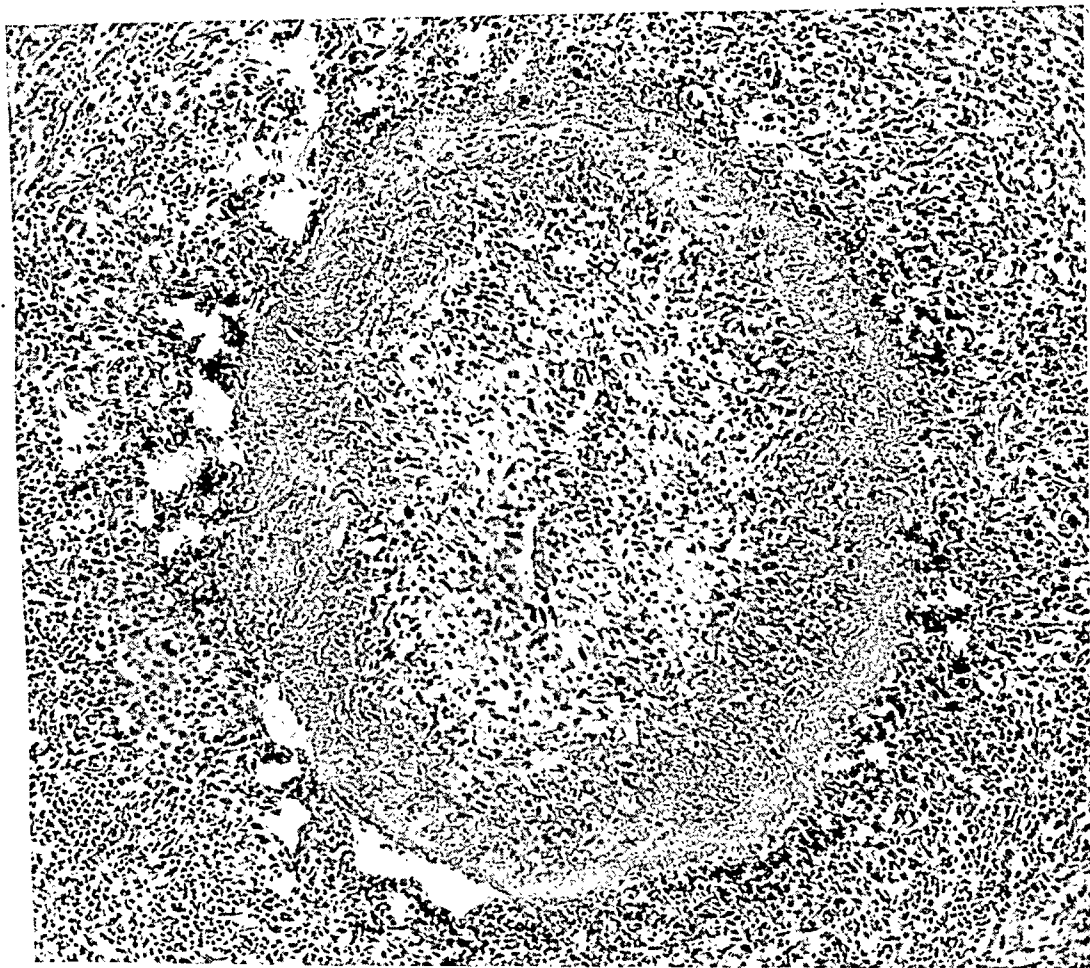


FIG. 5. Histological section of periadrenal vein showing diffuse phlebitis and periphlebitis with partial occlusion of the lumen. (Giemsa stain  $\times 400$ .)

perience to enable us to differentiate these various forms of muscle disease. Arteritis apparently occurs in an acute or accelerated form with a rapidly fatal outcome. According to Grant,<sup>18</sup> there is a more prolonged form in which the tempo of the disease is not only more tardy, but may be arrested and go on to the healing stage. In the accelerated variety, aneurysm formation and acute vascular lesions are found widely disseminated, and a fatality may follow the rupture of one of the former.

## PROGNOSIS AND TREATMENT

There has been no specific treatment for this disease. All of our patients died. Sulfonamide therapy was used in seven patients without any apparent improvement. Papaverine hydrochloride was useful as a vasodilator for the relief of peripheral arterial spasm. Other opiates were used in combination with salicylate therapy for the relief of pain. Despite our unhappy experience, an occasional patient may survive.

## SUMMARY

We have reported the clinical manifestations of periarteritis nodosa in a group of patients coming to autopsy. The disease should be considered a pathological entity. Fibrinoid necrosis of the media of the arteries and veins was observed, similar to the changes noted by Von Glahn and Pappenheimer<sup>10</sup> in the peripheral blood vessels in rheumatism, and by Klemperer, Pollack and Baehr<sup>20</sup> in disseminated lupus erythematosus.

## BIBLIOGRAPHY

1. KUSSMAUL, A., and MAIER, R.: Über eine bisher nicht beschriebene eigenthümliche Arterienkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsch. Arch. f. klin. Med.*, 1866, i, 484-518.
2. HARRIS, A. W., LYNCH, G. W., and O'HARE, J. P.: Periarteritis nodosa, *Arch. Int. Med.*, 1939, lxxiii, 1163-1182.
3. CHVOSTEK and WEICHSELBAUM: Herdweise syphilitische Endarteritis mit Aneurysmenbildung, *Allg. Wien. med. Ztg.*, 1877, xxii, 257-264.
4. GRUBER, G. B.: Zur Frage der Periarteritis nodosa, *Virchow's Arch. f. path. Anat.*, 1925, cclviii, 441-451.
5. RACKEMANN, F. M., and GREEN, J. S.: Periarteritis nodosa and asthma, *Trans. Assoc. Am. Phys.*, 1939, liv, 112-118.
6. VON HAUN, F.: Pathologisch-histologische und experimentelle Untersuchungen über Periarteritis nodosa, *Virchow's Arch. f. path. Anat.*, 1920, ccxxvii, 90-99.
7. HARRIS, W. H., and FRIEDRICH, A. V.: Experimental production of periarteritis nodosa in rabbits with a consideration of the causal excitant, *Jr. Exper. Med.*, 1922, xxxvi, 219-230.
8. MCCALL, MARSH, and PENNOCK, J. W.: Disseminated necrotizing vascularities—the toxic origin of periarteritis nodosa, *Am. Jr. Med. Sci.*, 1943, ccvi, 652-659.
9. OPHULS, W.: Periarteritis acuta nodosa, *Arch. Int. Med.*, 1923, xxxii, 870-898.
10. HERRMANN, W.: Pulmonary changes in a case of periarteritis nodosa, *Am. Jr. Roentgenol.*, 1933, xxix, 607-611.
11. LAMB, A. R.: Periarteritis nodosa: a clinical pathological review of the disease, *Arch. Int. Med.*, 1914, xiv, 481-516.
12. KLOTZ, O.: Periarteritis nodosa, *Jr. Med. Res.*, 1917, xxxvii, 1-49.
13. KOUNTZ, W. B.: Periarteritis nodosa, *Arch. Path.*, 1930, x, 55-58.
14. PASS, I.: Infarction of the liver, *Am. Jr. Path.*, 1935, xi, 503-525.
15. SPIEGEL, R.: Clinical aspects of periarteritis nodosa, *Arch. Int. Med.*, 1936, lvi, 993-1040.
16. ARKIN, A.: A clinical and pathological study of periarteritis nodosa, *Am. Jr. Path.*, 1930, vi, 401-426.

17. FRIEDBERG, C. K., and GROSS, L.: Periarthritis nodosa (necrotizing arteritis) associated with rheumatic heart disease, *Arch. Int. Med.*, 1934, liv, 170-198.
18. GRANT, R. T.: Observations on periarthritis nodosa, *Clin. Sci.*, 1940, iv, 245-275.
19. VON GLAHN, W. C., and PAPPENHEIMER, A. M.: Specific lesions of peripheral blood vessels in rheumatism, *Am. Jr. Path.*, 1926, ii, 235-249.
20. KLEMPERER, PAUL, POLLACK, A. D., and BAEHR, GEORGE: Pathology of disseminated lupus erythematosus, *Arch. Path.*, 1941, xxxii, 569-631.

## PERIARTERITIS NODOSA, WITH REPORT OF THREE CASES DIAGNOSED DURING LIFE\*

By SAUL SOLOMON, Major, M.C., MILOSH KASICH, Lt. Col., M.C., and  
NATHAN KIVEN, Major, M.C., *Fort Dix, New Jersey*

PERIARTERITIS nodosa is a disseminated but focal inflammatory disease of the smaller arteries, of unknown origin. It is almost invariably fatal. The true incidence of the disease is unknown since there can be no proof of the diagnosis except by histologic examination of tissues obtained by biopsy or at autopsy. It occurs with equal frequency in both sexes and is seen in all ages. The literature contains reports of approximately 300 cases, the great majority of which have been diagnosed post mortem. The increasing number of reports dealing with the subject in recent years indicates better recognition of the disease rather than an increased incidence. This report concerns three cases which were diagnosed during life and confirmed by biopsy, autopsy or both.

*Etiology.* The disease is inflammatory in nature but its etiology is unknown. It is certain that no one microorganism or toxin is exclusively responsible. It seems more likely that any one of a number of different agents may initiate or lead directly or indirectly to the disease. Rheumatic fever has been suggested by some authors<sup>1, 2, 3</sup> as the cause although the weight of evidence is against this. A more plausible explanation has been offered by Rich.<sup>4</sup> He described vascular lesions characteristic of periarteritis nodosa in five patients who, shortly before death, had hypersensitive reactions following therapeutic injections of foreign serum, and in one patient who had received prophylactic sulfathiazole treatment against aspiration pneumonia. Clark and Kaplan<sup>5</sup> reported two cases with similar vascular lesions following serum therapy. Other authors<sup>6</sup> have noted the association of the condition with asthma. The frequent occurrence of eosinophiles in the peripheral blood and in the specific lesions is further supportive evidence. Thus it would seem that the disease is an anaphylactic manifestation, the arterioles being the "shock organ." It is unnecessary then to look for a single direct explanation for all cases since many bacteria, drugs or toxins can act as the sensitizing agents leading to this disease.

*Clinical Picture.* The clinical picture of the condition is extremely varied, and symptoms referable to many systems of the body are found. A brief consideration of the pathologic anatomy of this condition is essential for a proper understanding of the clinical disease. The term periarteritis nodosa is misleading since not merely the adventitia but all the coats of the

\* Received for publication November 1, 1943.

From the Medical Services of Tilton General Hospital and Fort Dix Station Hospital, Fort Dix, New Jersey.

vessels are involved and node formations are by no means an essential part of the disease. The fundamental pathologic change is an inflammatory lesion involving the medium and smaller arteries. Inflammatory cells, chiefly polymorphonuclear leukocytes, eosinophiles and lymphocytes invade the adventitia and soon involve the media.

The four stages of the process are described as the degenerative, acute inflammatory, granulating and healing phases respectively. Different stages of the process may be seen simultaneously in an individual case. As a result of the arteritis, there may occur necrosis of the wall with hemorrhage, aneurysms or node formations, thrombosis with infarction and (as part of the healing phase) recanalization.

The clinical and laboratory findings separate themselves into four large groups. First there are those occurring from the inflammatory process, such as fever, leukocytosis, general malaise, loss of weight, rapid sedimentation rate, anemia, and in general the picture of fever or sepsis of unknown origin.

Secondly one sees the symptoms which arise from the involvement of the arteries of particular organs, such as the heart (evidences of coronary artery disease, myocardial infarctions, heart failure), nervous system (peripheral neuropathy, visual disturbances, headaches), gastrointestinal system (abdominal cramps, vomiting, anorexia, bleeding, diarrhea), or kidneys (albuminuria, hematuria, azotemia, hypertension). It is thus seen that any system and in fact all systems may be involved leading to almost any combination of symptoms that the imagination can conceive. It is this irregular and baffling symptomatology which has resulted in such confusion and misdiagnosis during life. But if one gives the matter careful consideration the very protean nature of this symptom complex should lead one to consider this condition in the differential diagnosis of fevers of unknown origin.

The eosinophilia in the peripheral blood (in 15 to 20 per cent of the cases) and in the histologic sections of the involved arteries comes under a separate category probably representing an allergic manifestation. Two of our three cases had eosinophilia which was not marked—6 per cent and 7 per cent respectively. The incidence of eosinophilia will vary with the frequency with which differential white cell counts are done.

Palpable nodules along the course of subcutaneous vessels are helpful diagnostically when present, but they are not common. Two of our three cases had such nodules. Finally, in suspicious cases, a biopsy of a muscle should be done and careful histologic examination made of vessels in the removed tissue. The clinician should accept with caution a negative report since, as was noted in one of our cases, three separate biopsies failed to show any significant changes, although at autopsy there was no doubt about the diagnosis. Findings such as these serve to emphasize the focal nature of the disease.

Specialists in different branches of medicine have reported the disease

as simulating well known clinical entities. Allen<sup>7</sup> reported an instance which simulated an acute abdominal inflammation so closely that operation was performed before the diagnosis was made. Wechsler and Bender<sup>8</sup> have written an excellent report on the neurological manifestations of periarteritis nodosa emphasizing the predominance of peripheral nerve lesions. One author<sup>9</sup> has even described a sigmoidoscopic diagnosis of the disease. For more complete descriptions of the clinical findings, the reader is referred to articles by Baker,<sup>10</sup> Jones,<sup>11</sup> and Appelbaum and Kalkstein.<sup>12</sup>

*Treatment.* There is no known therapy for the disease. Goldman, Dickens and Schenken<sup>13</sup> reported the apparent cure of a case with sulfa-pyridine. This must be viewed with some skepticism in view of the fact that occasional instances of spontaneous recovery have been reported.<sup>14</sup> Indeed, the finding of healed (recanalized) arteritis in routine autopsy studies is not a very rare occurrence. Since no specific therapy can be suggested, the treatment must be supportive and symptomatic. In view of the theory that allergy is the background of this disease, a careful search for an allergen in individual instances would seem to be in order. However it is questionable whether removal of the allergen or desensitization would serve any therapeutic purpose. In one of our cases there was a positive finding of lead poisoning and in another instance the illness was preceded by an upper respiratory infection. In all three of our cases, by the time the disease was diagnosed, it was too far advanced to give any form of therapy a reasonable chance for success.

The following are the clinical protocols and brief autopsy findings of the three cases seen.

#### CASE REPORTS

*Case 1.* A. D., a white soldier, aged 38, became ill during the first week of May 1942, with pain in the back of the legs and arms, for approximately five days following exposure to rain and cold. There was also a history of loss of weight. The past history was irrelevant except for the fact that he had formerly worked as a painter.

He was admitted to Fort Dix Station Hospital on May 12, 1942, appearing pale, asthenic, and poorly nourished. Temperature was 99.6° F., and pulse rate 110. The upper respiratory tract and mouth were normal. The lungs were clear both on physical and roentgenographic examinations. The heart rhythm was regular and no murmurs were heard. The blood pressure was normal. Abdominal examination including rectal was negative. He had pain and tenderness in the calves, thighs and biceps with no objective findings. The blood cell count showed 4,250,000 red cells with 80 per cent hemoglobin; the white cell count was 7,800 with 59 per cent polymorphonuclears and 31 per cent lymphocytes. The urine had a specific gravity of 1.030 and no albumin or sugar was noted. The microscopic examination was negative. Kahn reaction was negative. The sedimentation rate was 5 mm. per hour (Cutler method). The blood sugar, urea nitrogen, chlorides and Van den Bergh were normal.

The admission diagnosis was myositis, but his condition did not improve on bed rest and salicylates. During the first week of June he complained of anorexia and abdominal cramps. His temperature ranged from 99° F. to 100° F. by mouth. The

sedimentation rate was then 44 mm. per hour and the white cell count had risen to 10,400 with a normal differential. The patient reported that one urine specimen was dark and smoky but the sample had already been discarded. Some nodules were felt along the course of the brachial arteries. A biopsy of the right biceps was done with negative findings.

Although he had no cardiac symptoms, an electrocardiogram was made which showed low T waves in Leads I and III. This was interpreted as suggesting myocardial damage. A clinical diagnosis was made of periarteritis nodosa although the biopsy had failed to confirm it.

Early in July he complained of numbness of both legs, and it was noted that he had foot drop on the left and decreased sensation to all modalities below the knee bilaterally, more marked on the left. On August 9, he had a generalized convulsion and the fundi showed papilledema. He fell out of bed and suffered contusions about the face. This event was one of the factors that led the neurosurgeon, at a later date, to consider the possibility of a subdural hemorrhage to account for certain of his neurologic findings.

The blood pressure on August 10 was found to be 220 mm. Hg systolic and 140 mm. diastolic. The spinal fluid showed 40 white cells per cubic millimeter, of which 70 per cent were polymorphonuclears and 30 per cent were lymphocytes. The Pandy and Kahn tests were negative but the colloidal gold curve was 5554321000.

The patient became more confused and dull and complained of severe frontal headaches. He was transferred to Tilton General Hospital on August 13, because of the possibility of an expanding intracranial lesion. A bilateral occipital trephination was done on August 15 with negative findings.

At that time the white cell count was 10,200 with 63 per cent polymorphonuclears of which 8 per cent were young forms, 28 per cent lymphocytes, 6 per cent eosinophiles, 2 per cent monocytes and 1 per cent basophiles. The specific gravity of the urine was 1.022 and a trace of albumin was found. There were a few casts and white cells present per high power field. The blood chloride level was 373 mg. per cent but the other chemical constituents of the blood were normal. The electrocardiogram showed low voltage of the T waves in Leads I and II and slight inversion in Lead III. A muscle biopsy done on August 15 showed normal findings.

His history of having worked as a painter led us to consider the possibility of plumbism as the most likely diagnosis after periarteritis nodosa since this condition could explain the cramps, vomiting, hypertension, foot drop and convulsions. The fact that he had been away from his occupation for more than one and a half years did not exclude the diagnosis. He had, partly by choice, been on a low calcium diet which would tend to mobilize any stored lead from the bones into the blood. There was some stippling of the red cells on one smear but no lead line was found on the gums. A twenty-four-hour urine specimen showed 12 gamma per cent of lead which was considered diagnostic of plumbism.

The patient continued a downward course and became more stuporous. On August 26 blood was found to be oozing from the right trephine incision and approximately 25 c.c. of dark blood and clots were expressed from the incision. The patient died on August 27.

The autopsy showed massive bilateral subdural hemorrhages which were considered as probably due to the trephine operation, a rather unusual complication. There were also old and recent pontine hemorrhages. The pia mater over the frontal lobes was fibrinous and thickened. The blood vessels of most of the organs studied showed varying degrees of inflammatory thickening, fibrinous degeneration, muscular disruption, vessel occlusion with recanalization and infiltration of the vessel walls with various inflammatory cells, lymphocytes, plasma cells, histiocytes, eosinophiles, and polymorphonuclear cells. The histologic appearance was characteristic of peri-



arteritis nodosa. The lesions were diffuse but patchy, and different stages of the process were observed, a few vessels showing acute inflammation but most of them showing the healing phase. The following organs were found to be involved: the heart (small coronary vessels), the liver, gall-bladder, spleen, pancreas, adrenals, kidneys, testicles, lumbosacral nerve plexus, and vessels of the brain.

*Case 2.* J. M., a white soldier, age 47, was admitted to Tilton General Hospital on August 19, 1942, complaining of pain in the abdomen, loss of weight, fever, pain in the legs, weakness and chronic cough since June 1942. The past history was irrelevant. His habits were not significant except that he smoked 20 cigarettes daily. Because of the history of abdominal complaints, positive guaiac test in the stools and the barium enema which showed poor filling of the descending colon, a diagnosis had been made of carcinoma of the descending colon at his previous station.

On admission he appeared emaciated, temperature was 99° F., pulse 130, respirations 20. The skin was pale, dry and scaly. There was moderate clubbing of the fingers and some ankle edema. The mouth was edentulous. He formerly had worn false teeth but had lost them during a bout of seasickness in January 1941 on his way to Newfoundland and had never attempted to acquire a new set. The heart was rapid and showed occasional premature contractions. No murmurs were heard. The blood pressure was 146 mm. Hg systolic and 78 mm. diastolic. An electrocardiographic tracing on the following day showed an iso-electric T wave in the first lead and inverted T waves in the second and third leads. Wheezes and rhonchi were heard in both lungs. The abdomen was scaphoid and no abnormal masses were felt. The liver was three fingers' breadth below the costal margin. Neurologic examination showed diminished knee-jerks and absent ankle-jerks. There was a bilateral foot drop and glove and stocking hypesthesia of all extremities. The fundi showed changes of arteriosclerosis and small old hemorrhages in the left eye.

The urine had a specific gravity of 1.012 and contained one plus albumin (0.031 per cent), and 5 to 6 white cells per high power field. The blood chemistry values were essentially normal with the exception of serum albumin and globulin. The serum albumin was 2.8 grams per 100 c.c. of blood and the serum globulin was 3.24 grams. That ratio was maintained with minor variations throughout his illness. The red cells on admission numbered 4,600,000; the white cells numbered 12,800 with 70 per cent polymorphonuclears, of which 17 per cent were young forms, 27 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophiles. The white cell count was never markedly elevated, although on one occasion in December it reached 16,600. The maximum shift to the left of the Schilling index was 30 per cent young forms; the highest percentage of eosinophiles noted was 7 per cent. The blood sedimentation rate was 26 mm. per hour by the Cutler method and remained elevated throughout the illness. The spinal fluid obtained on September 4 was normal.

Roentgenograms of the chest were normal with the exception of congestive changes at the base of the lungs. The gastrointestinal roentgenograms and barium enema were normal. Gastric analysis showed absolute achlorhydria.

At first it was thought that his emaciation and peripheral neuropathy were due to vitamin deficiency since he had been without teeth since January 1941. However, he continued to have an irregular fever of 98 to 102° F., and failed to improve despite the use of massive doses of vitamins. Hence, on October 13, 1942, for the first time a diagnosis of periarteritis nodosa was made on clinical grounds. A biopsy of the left gastrocnemius muscle was done on October 21. The pathologist reported finding muscular degeneration and diffuse disease in the small arteries characterized by thickening and thrombosis with some perivascular infiltration with lymphocytes and histiocytes, which he stated would be compatible with the healing phase of periarteritis nodosa. A second biopsy of the gastrocnemius muscle was done three weeks

later and showed similar changes except that the vascular changes were more severe and appeared to be more inflammatory in character.

When the patient first came under observation he had hypostatic pulmonary congestion, enlargement of the liver, edema of the ankles, and markedly increased circulation time. The T wave was iso-electric in Lead I and inverted in Leads II and III. These signs and symptoms did not change following digitalization and bed rest. He had several transfusions which did not improve his condition materially. On November 23, he had severe pain and tenderness over the testicles which were relieved by sedation and the use of an adhesive support. On December 26 it was noted that he had petechiae on both arms and hands. The clinical course was progressively downward. A pericardial friction rub was heard on January 29. He developed pulmonary edema and died on January 30, 1943.

At autopsy the outstanding gross finding was marked wasting and atrophy of all body structures and viscera, except for the heart which showed moderate hypertrophy. Acute serofibrinous pericarditis was present as well as periarteritis nodosa of the smaller branches of the coronary arteries, with microscopic myocardial infarctions both old and recent.

Microscopically, vascular lesions of periarteritis nodosa were found widely disseminated; some of the vessels showed acute lesions whereas others showed the healing stage with thrombosis and recanalization. Infarctions were found in the liver and kidneys. The vessels of the peripheral nerves and of the testicles and prostate were found to be involved which adequately explained certain of the prominent clinical symptoms.

*Case 3.* F. M., a white male, age 26, was admitted to Fort Dix Station Hospital on April 15, 1942 with a complaint of generalized muscular aches and pains of four days' duration. On examination he had an injected throat and tenderness of the muscles around the elbows. The rest of the examination was negative. The heart rate was rapid and a soft systolic murmur was heard at the apex. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The electrocardiogram was normal. Roentgenogram of the chest was normal. The sedimentation rate was normal. Urinalysis showed a specific gravity of 1.026, no albumin or sugar, but some white and red blood cells. The blood count was 4,980,000 red cells with 90 per cent hemoglobin and 8,000 white cells (differential count not done). The blood chemistry including serum albumin and globulin was normal. The patient had a persistent low grade fever and the usual agglutination tests were negative.

On May 6, he complained of pain in the right testicle and burning pain on urination which subsided spontaneously in a few days. On May 17, he complained of chest pain and abdominal cramps and it was noted that he had lost 23 pounds. He also had numbness of the right first, second and third fingers and developed nodules on the medial aspect of the right arm and along the shins and ankles. He continued to show a septic type of fever and developed stiffness and numbness of the hands and feet. The red cell count was unchanged, but he now had a leukocytosis of 16,200 with 81 per cent polymorphonuclears and 19 per cent lymphocytes. The diagnosis of periarteritis nodosa was postulated and a biopsy of the right gastrocnemius was done which showed several thickened blood vessels infiltrated with polymorphonuclear cells and lymphocytes surrounded by fibrous tissue. One vessel, a vein, was thrombosed and partly recanalized. The pathologic diagnosis was made of periarteritis nodosa.

The temperature became higher and more irregular and the numbness in the extremities increased, particularly in the left foot. He complained of severe abdominal cramps and pain in the elbows and ankles. On June 12, he became cold, clammy and nauseated and had pin-point pupils. Tympanites developed, the pulse became imperceptible, and he gasped for breath. Death occurred that evening.

At autopsy the immediate cause of death was found to be acute massive subcapsular hemorrhage of the left kidney and the right lobe of the liver. The heart was normal. The lungs showed moderate hypostatic congestion. There were several sharply outlined areas of hemorrhage in the spleen. There were lesions characteristic of periarteritis nodosa in the smaller blood vessels of the diaphragm; the ileum, liver, spleen, pancreas and kidneys.

### SUMMARY

Three cases of periarteritis nodosa diagnosed during life and confirmed at autopsy are reported. The clinical features and differential diagnosis are discussed. The diagnosis should be considered in patients with prolonged fever of unknown origin who have irregular and baffling symptoms referable to many systems of the body. A biopsy of any readily accessible tissue such as the gastrocnemius muscle will usually reveal characteristic changes in the smaller arteries. Negative findings do not eliminate the possibility of periarteritis nodosa.

The etiology of the disease is unknown though it seems likely that the disease occurs as an allergic reaction to many different antigens, the arterioles being the shock organ. There is no specific treatment. Most of the well advanced and recognizable cases end fatally.

### BIBLIOGRAPHY

1. FRIEDBERG, C. K., and GROSS, L.: Periarteritis nodosa associated with rheumatic heart disease, *Arch. Int. Med.*, 1934, liv, 170.
2. OPHULS, W.: Acute periarteritis nodosa, *Arch. Int. Med.*, 1923, xxxii, 870.
3. SPIEGEL, R.: Clinical aspects of periarteritis nodosa, *Arch. Int. Med.*, 1936, lviii, 993.
4. RICH, A. R.: The role of hypersensitivity in periarteritis nodosa, *Bull. Johns Hopkins Hosp.*, 1942, lxxi, 123.
5. CLARK, E., and KAPLAN, B. I.: Endocardial, arterial and other mesenchymal alterations associated with serum disease in man, *Arch. Path.*, 1937, xxiv, 458.
6. RACKEMANN, F. M., and GREEN, J. E.: Periarteritis nodosa and asthma, *Trans. Assoc. Am. Phys.*, 1939, liv, 112.
7. ALLEN, P. D.: Periarteritis nodosa simulating an acute abdominal condition requiring operation, *Arch. Surg.*, 1940, xl, 271.
8. WECHSLER, I. S., and BENDER, M. B.: The neurological manifestations of periarteritis nodosa, *Jr. Mt. Sinai Hosp.*, 1942, viii, 1071.
9. FELSEN, J.: The sigmoidoscopic diagnosis of periarteritis nodosa, *Ann. Int. Med.*, 1941, xv, 251.
10. BAKER, L. T.: Periarteritis nodosa with report of two cases, *Ann. Int. Med.*, 1942, xvii, 223.
11. JONES, G. M.: Periarteritis nodosa with case reports, *Ann. Int. Med.*, 1942, xvi, 920.
12. APPELBAUM, E., and KALKSTEIN, M.: Periarteritis nodosa, *New York State Jr. Med.*, 1939, xxxix, 2253.
13. GOLDMAN, B. A., DICKENS, N. L., and SCHENKEN, J. R.: The apparent cure of periarteritis nodosa with sulfapyridine, 1941, cciv, 443.
14. VINING, C. W.: A case of periarteritis nodosa with subcutaneous lesions and recovery, *Arch. Dis. Child.*, 1938, xiii, 13.

# AN ELECTROCARDIOGRAPHIC STUDY OF CARDIAC AGING BASED ON RECORDS AT REST AND AFTER EXERCISE\*

By MILTON MAZER, Captain, M.C., A.U.S., and JOHN A. REISINGER,  
Lieutenant Commander, M.C., U.S.N.R., F.A.C.P.,  
*Washington, D. C.*

It is often assumed that changes in the heart accompanying the aging process may be mirrored by the electrocardiogram, and that tracings in aged individuals should be interpreted with less rigid criteria than in the young. There is actually little evidence to support this view. Most of the studies which purport to show more electrocardiographic abnormalities in the later age groups are based on either "non-cardiac hospital patients" or on series of routine tracings of inadequately studied individuals. The careful study of Larsen and Skulason<sup>1</sup> avoided most of the sources of error of previous investigations. In a group of 100 normal persons divided equally between the fourth and fifth decades they found little evidence for cardiac aging. The only statistically significant differences between the two age groups were the greater frequency of a saddle-shaped S-T segment and left axis deviation in the older. It must be noted that the age difference between the two groups was only 10 years.

It has been thought that the imposition of a strain upon the heart might bring out electrocardiographic evidence of latent myocardial damage, and there is experimental support of this view.<sup>2</sup> In the main two methods have been used for the imposition of such strain, namely, oxygen deprivation and exercise. Because the rebreathing method used in the initial investigations<sup>3, 4</sup> induces an altering and uncontrolled degree of oxygen deficiency, Levy, Barach and Bruenn<sup>5</sup> devised an apparatus capable of providing a constant proportion of oxygen in the inspired air. In this and another study<sup>6</sup> Levy and his associates showed that oxygen deficiency so induced could cause T-wave depression and S-T segment deviation in normal individuals. Since the effects were often greater in patients with evidence of coronary insufficiency they set up criteria for a normal response, suggesting the use of the method as a test for coronary insufficiency. Larsen<sup>7</sup> published the results of a similar study.

Burnett, Nims and Josephson<sup>8</sup> administered a 10 per cent oxygen mixture (at the altitude of Denver, Colorado) to normal subjects between 21 and 60 years of age but were able to show no significant differences in the electrocardiographic responses in the various age groups. In brief, no evidence for the existence of cardiac aging was demonstrated by this method.

\* Received for publication May 26, 1943.

From the Cardiovascular Research Unit, Veterans Administration Facility. Published with the permission of the Medical Director of the Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

In an earlier publication, May<sup>9</sup> had reported that "the effect of oxygen deficiency, as measured by diminution in the height of the T-waves, lessens considerably with advancing age." The validity of May's conclusion has been questioned by Burnett and his associates.<sup>8</sup> Since he used the rebreathing method May was not able to state the degree of oxygen deprivation to which his patients were subjected, and in view of the fact that the metabolic rate is generally higher in younger individuals, it seems likely that his younger patients were subjected to greater anoxic stress than the older.

The effects of exercise on the electrocardiogram of normal individuals have been studied,<sup>10, 11, 12</sup> and the response of the T-waves and S-T segments described. The degree and frequency of electrocardiographic change produced by exercise are generally greater in patients with diseased hearts. This method has apparently not been used to study cardiac aging.

The present study had two objects: first, to determine whether the electrocardiographic exercise response would give evidence of cardiac aging, and second, to establish standards for the electrocardiographic response to exercise in a sufficient number of normal individuals.

#### EXPERIMENTAL SUBJECTS

All of the subjects were men. The younger group consisted of 44 young adults who were applicants for the position of U. S. Border Patrolman. They ranged in age from 21 to 33 with an average of 24.8 years. Because of the standards of the examination the minimum height was 68 inches; the maximum was 75.25 inches with an average of 70.5. The weight range was 132 to 223 pounds (average 170).

The older group consisted of 44 veterans of World War I who were applicants for U. S. Government Life Insurance. They varied in age from 39 to 56 years (average 46), in height from 63 to 73 inches (average 67.4) and in weight from 112 to 219 pounds (average 158).

Each individual was subjected to a complete history and physical examination. In addition, a urinalysis, blood Wassermann and Kahn tests, and a teleroentgenogram of the heart were done in each case. Only individuals who were normal by these criteria and whose resting blood pressures were below 150 systolic and 90 diastolic were included. Because of the nature of the examinations for which they were applicants, it was realized that there might be reticence in the free disclosure of symptoms on effort. An attempt to elicit such symptoms was made by a discussion of extra-vocational interests, hobbies and recreational activities of an athletic nature. Moreover, each individual was subjected to a two-step exercise test without producing unusual symptoms.

#### TECHNIC

The records were made on a vacuum tube amplifier-oscillograph type of instrument. The sensitized paper was run at the standard rate of 25 mm.

per second and the instrument standardized for a deflection of 1 cm. per millivolt. The timer was checked and found to be running 1.5 per cent slow. Records were taken from the three standard limb leads and one chest lead, CF-4, with the patients lying supine. The chest electrode was circular and 3 cm. in diameter. Its position on the chest was marked so that it might be accurately reapplied after the exercise. The patients were exercised with the limb electrodes in place, the lead connections being disconnected. As soon as the exercise was completed the patient resumed his former position on the table. The lead connections were made and Leads IV, I, II and III were taken in order. The electrocardiograms were recorded within three minutes of the cessation of the exercise. The exercise consisted of ascending and descending a standard two-step staircase as many times as each patient was able within 90 seconds. The average number of trips was 41.8 in the younger group and 35.2 in the older. No patient made fewer than 30 trips, none more than 48.

The readings were made from the records with the aid of a magnifying glass whenever necessary. The height of several waves in each lead was measured to the nearest 0.025 mv. or one quarter of the smallest voltage unit on the tracings. The time intervals were measured to the nearest 0.01 sec. In cases where the voltage varied phasically, due to respiratory movements, the range was recorded and the average computed. In cases in which sinus arrhythmia was present the longest and shortest R-R interval with their corresponding QRS and QT intervals were noted and averaged. The electrical axis was determined for each record by plotting the R and S waves in Leads I and III on the Einthoven triangle in the usual manner.

## RESULTS

*The Electrocardiogram at Rest.* A comparison of the electrocardiograms of the two age groups taken at rest reveals few significant differences. Sinus arrhythmia was somewhat more frequent in the younger group. The P-waves and P-R intervals were not significantly different. Discernible Q-waves in Leads I and II did not occur with significantly greater frequency in either group. A discernible Q-wave in Lead III occurred in 28 records of the younger group and in 17 of the older, a difference which the chi-square test indicates is statistically significant. The greater frequency of Q-waves in Lead III in the younger group is probably due to the greater tendency to right axis deviation in the group.<sup>13</sup> There was only one Q-wave in Lead III that was significantly deep by Pardee's criteria.<sup>13</sup> It was found in an older subject with a transversely placed heart and since its depth varied with respiration it is probably of no significance.<sup>14</sup> The average R-wave was of lower voltage in Lead I and of higher voltage in Leads II and III in the younger than in the older group. Related to this was the greater tendency to a "rightward" electrical axis (Einthoven) in the younger group. The average angle for this group was 59.0°, with a standard deviation of  $\pm 23.5$ .

In the older group the average angle was  $42.8^\circ \pm 27.3$ . The difference is statistically significant. There was no significant difference between the two groups in the duration of the QRS complex.

Elevation of the S-T segment of 0.5 or more in the limb leads occurred in five instances, all in Lead II in the younger group. Depression of the segment below the isoelectric line was never more than 0.5 mm. The frequency of S-T interval depression was not significantly different in the two groups. As shown in table 1 the average height of the T-wave was greater

TABLE I  
Height of T-Waves before and after Exercise

Leads	Younger Group		Older Group	
	Before Exercise	After Exercise	Before Exercise	After Exercise
I	2.12	1.85	1.77	1.39
II	2.84	3.23	2.32	2.47
III*	1.37	1.66	1.16	1.38
CF-4	4.69	5.45	4.40	5.24

\* Cases in which waves are positive.

in the younger group in each of the four leads, but only the differences in Leads I and II are statistically significant. The greater height of the T-wave in Leads I and II in the younger group assumes even greater significance when it is recalled that the electrical axis in this group was more "rightward" than in the older. The Q-T interval was not significantly different in the two groups. A linear formula was fitted to the entire data by the method of least squares after correction for the — 1.5 per cent error in the timer. The formula was

$$QT = 0.15 \times R-R \text{ plus } 0.22$$

*The Electrocardiogram after Exercise.* A. The Effects of Exercise within Each Group.

Sinus arrhythmia first appeared after exercise in two cases in the younger group and in six in the older. In the 13 records in the younger group in which it was present at rest it disappeared after exercise in five. It persisted after exercise in the one case in the older group.

The changes in the P-wave due to exercise were not significantly different in the two groups. It often decreased in voltage in Lead I and increased in Leads II and III. The maximum increase was 1.25 mm. Inversion of the P-wave after exercise occurred only once in Lead I and no times in Lead II. Changes in direction were frequent in Leads III and CF-4.

The P-R interval usually decreased in each lead in both groups after exercise. The decrease was generally greatest in Lead IV. This is probably due to the faster rate in this lead since it was the first taken after exercise.

The QRS complex was almost always diphasic or triphasic both before and after exercise. The monophasic complexes which did occur were always upright. The presence of discernible Q-waves was not markedly affected by exercise. A significantly deep Q-wave in Lead III was seen in two records after exercise; in one it had also been present at rest. Statistically significant changes in the voltage of the R-wave due to exercise occurred only in Leads I and CF-4 in each group. In both groups the waves became lower in voltage in both of these leads.

The average electrical axis in the younger group became more "rightward" after exercise. Changes of more than  $5^\circ$  to the right were seen in 32 cases and to the left in one. In the older group changes in both directions were common. Eighteen cases became more "rightward" and 14 more "leftward." The average change for the group was not significant.

The changes in the average duration of the QRS complex were minimal. It appeared to increase slightly in the limb leads and decrease slightly in the chest lead, but the changes were too small to be considered significant.

Depression of the S-T segment by exercise to below the isoelectric line from an initially positive or isoelectric position was seen in one or more limb leads in 49 tracings of the entire series. It was most often seen in Lead II, 33 times. In the chest lead it occurred in nine records. In the limb leads the S-T segment depression was greater than 0.75 mm. in only one record. In CF-4 the depression was greater than 0.75 mm. in seven cases; the greatest depression was 1.75 mm. Most often the depression in each lead was 0.25 mm.

T-wave inversion in either Leads I, II and CF-4 occurred only once after exercise. A T-wave in Lead I of 4 mm. became  $-0.25$  mm. after exercise. There was no reason to question the normality of this subject. The single diphasic T-wave in CF-4 became upright after exercise. Changes in T-wave voltage of 0.5 mm. or more occurred frequently in those leads in which T is normally highest, namely, Leads II and CF-4. Most often  $T_1$  became lower in voltage while  $T_2$ ,  $T_3$  and  $T_4$  became higher. The changes in Leads I and III were generally reciprocal in any one record. The average voltage of the T-waves before and after exercise in each group is given in table 1. The T-wave in Lead I appeared to become lower in voltage while those in Leads II, III, and CF-4 became higher after exercise. These changes are statistically significant in each instance except for  $T_2$  in the older group. The statistical analysis was performed by solving for  $t$  by means of Fisher's method<sup>15</sup> for a unique sample. It is interesting to note that the average T-wave changes were opposite in direction in Leads I and CF-4.

The Q-T interval after exercise altered with the increase in rate. However, a linear formula fitted to the after exercise data by the method of least squares did not differ significantly from that for the control tracings.

*B. Comparison of Changes in Younger and Older Groups.*



The magnitude of the changes in the electrocardiograms due to exercise were compared in the younger and older groups by the appropriate statistical methods. The change in the voltage of the various waves was considered significant when the mean difference between the two groups was more than twice the standard deviation of their means. The frequency of various changes was compared by applying the chi-square test to a fourfold table. Differences giving a chi-square of more than 3.8 were considered significant.

The changes in the components of the electrocardiogram due to exercise were generally of the same order of magnitude in the younger and older groups. In only a few components were the differences between the two groups statistically significant. The changes due to exercise in the younger and older groups were not significantly different in respect to the duration of the P-R and QRS intervals, the P- and T-waves, and the R-waves in Leads I, III and CF-4. In Lead II the decrease in voltage of the R-waves in the younger group was significantly greater than in the older. The frequency of S-T segment depression in one or more of the limb leads was significantly greater in the older group. Such S-T segment depression was seen in 35 records of the older group and in 14 of the younger. The changes in the T-wave due to exercise were not significantly different in the two groups.

### DISCUSSION

The present study demonstrates but few significant differences between the electrocardiograms of males in the third and fifth decades. In tracings taken at rest significant differences between the two age groups were found only in the frequency of Q-waves in Lead III, the voltage of the R-waves in the limb leads, and the voltage of the T-waves in Leads I and II. The Q- and R-wave differences are to be related to the greater tendency to "rightward" deviation of the electrical axis in the younger group. The difference in electrical axis is probably due to a difference in the position of the heart. It should be noted the average height was less in the older group. The smaller height of the T-waves in Leads I and II in the older group must be considered to be indicative of cardiac aging, since any T-wave differences due to the variation in the electrical axis should be in the opposite direction. The analysis of the records secured after exercise gives additional evidence for cardiac aging. Significant S-T interval depression occurred more often in the older age group.

Both of these differences, namely, the lower T-waves in Leads I and II and the greater frequency of S-T segment depression, are considered evidence of a lessened myocardial efficiency in the older subjects as compared with the younger. The known effect of myocardial disease on the T-wave and S-T segment supports this view. In addition, the administration of oxygen which may be presumed to increase myocardial efficiency, often increases the voltage of T-waves in normal subjects.<sup>16</sup> The studies on oxygen

deprivation and exercise cited above have shown that S-T segment depression is one of the characteristics of coronary artery disease.

One of the primary purposes of the present study was to establish criteria for a normal response of the electrocardiogram to standard exercise. It is obvious that if such a test is to be useful in the recognition of coronary insufficiency, the complete range of response of the normal individual must first be known. It has been found in the present study that though the alterations in the QRS complex due to exercise show definite average trends, there are individual variations in either direction. Hence, definite criteria for the normal variation of this component cannot be established. With the S-T segment the situation is quite different. The changes after exercise were more constant and the variations from the average were small. Except for the T-wave in Lead I in one case, all of the T-waves in Leads I, II and IV were upright after exercise. Low voltage of the T-waves in all of the limb leads or in the chest lead was not seen after exercise.

From the data of the present study the following criteria for an abnormal electrocardiographic response to standard exercise in the age groups considered are suggested:

- (1) Depression of the S-T segment by exercise of more than 0.75 mm. in Lead I, 1.5 mm. in Lead II, 0.75 mm. in Lead III, and 1.75 mm. in Lead CF-4.
- (2) Inversion of the T-waves in Leads I, II or CF-4.
- (3) Low voltage of the T-waves in all of the limb leads.

Criteria 1 and 2 would appear to be the most useful and dependable. The criterion for the S-T interval depression is based on the extreme depression seen in this series. Application of the statistical method with a range of three times the standard deviation from the mean gives substantially the same values as the extremes. Since, in general, the greatest degree of depression occurred in those cases in which the segment was slightly elevated initially, the final deviation after exercise was slightly less than the extremes given above. The criteria for the S-T interval change in this study are slightly more rigid than in that of Twiss and Sokolow.<sup>12</sup> It must be noted, however, that the "normals" in their study apparently included patients with heart disease (though not angina pectoris).

#### SUMMARY

The changes in the normal heart due to aging have been investigated by comparing the electrocardiograms taken at rest and after exercise in 88 normal men divided equally between the third and fifth decades. The data were treated by appropriate statistical methods and the significant differences between the two age groups determined. The differences which are considered evidence of cardiac aging are noted and discussed. Criteria are suggested for the electrocardiographic response to standard exercise in normal subjects.

## BIBLIOGRAPHY

1. LARSEN, K., and SKULASON, TH.: The normal electrocardiogram. I. Analysis of the extremity deviations from 100 normal persons whose ages ranged from 30 to 50 years, *Am. Heart Jr.*, 1941, xxii, 625.
2. SCOTT, W. S., LESLIE, A., and MULINOS, N. G.: Studies on coronary occlusion. I. The effects on the electrocardiogram of the cat of producing anoxemia after coronary ligation, *Am. Heart Jr.*, 1940, xix, 719.
3. GREENE, C. W., and GILBERT, N. C.: Studies on the responses of the circulation to low oxygen tension. III. Changes in the pacemaker and in conduction during extreme oxygen want as shown in the human electrocardiogram, *Arch. Int. Med.*, 1921, xxvii, 517.
4. ROTHSCHILD, M. A., and KISSIN, M.: Induced general anoxemia causing S-T deviation in the electrocardiogram, *Am. Heart Jr.*, 1933, viii, 745.
5. LEVY, R. L., BARACH, A. L., and BRUENN, H. G.: Effects of induced oxygen want in patients with cardiac pain, *Am. Heart Jr.*, 1938, xv, 187.
6. LEVY, R. L., BRUENN, H. G., and RUSSELL, N. G.: The use of electrocardiographic changes caused by induced anoxemia as a test for coronary insufficiency, *Am. Jr. Med. Sci.*, 1939, cxcvii, 241.
7. LARSEN, K. H.: On electrocardiographic changes in health and disease during experimental anoxemia, 1938, Iltmangel, Copenhagen.
8. BURNETT, C. T., NIMS, M. G., and JOSEPHSON, C. J.: The induced anoxemia test, a study by age groups, *Am. Heart Jr.*, 1942, xxiii, 306.
9. MAY, S. H.: Electrocardiographic response to gradually induced oxygen deficiency. I. Response of normal hearts in various age groups, *Am. Heart Jr.*, 1939, xvii, 665.
10. RISEMAN, J. E. F., WALLER, G., and BROWN, M. G.: The electrocardiogram during attacks of angina pectoris: its characteristics and diagnostic significance, *Am. Heart Jr.*, 1940, xix, 683.
11. SIGLER, L. H.: Electrocardiographic changes induced by exercise in the diagnosis of coronary insufficiency, *Jr. Lab. and Clin. Med.*, 1940, xxv, 796.
12. TWISS, A., and SOKOLOV, M.: Significant electrocardiographic changes following exercise, *Am. Heart Jr.*, 1942, xxiii, 498.
13. PARDEE, H. B.: The significance of an electrocardiogram with a large Q in Lead 3, *Arch. Int. Med.*, 1930, xlvi, 470.
14. VIDELA, J. G.: La onda Q profunda en la III derivacion del E. C. G. Importancia de sus variaciones durante la inspiracion profunda, *Rev. argent. de cardiol.*, 1939, vi, 146.
15. FISHER, R. A.: Statistical methods for research workers, 1941, Oliver and Boyd, London.
16. BARACH, A. L., and STEINER, A.: The physiologic action of oxygen and carbon dioxide on the coronary circulation as shown by blood gas and electrocardiographic studies, *Am. Heart Jr.*, 1941, xxii, 13.

# LEUKOCYTOSIS AND THE SYMPATHETICO-ADRENAL SYSTEM \*

By F. B. CLARE, C. H. CRESS, and E. GELLHORN,† *Chicago, Illinois*

ALTHOUGH leukocytosis has often been linked with the excitation of autonomic centers and the secretion of epinephrine (Müller,<sup>1</sup> Hoff<sup>2</sup>) actual proof for this mechanism is rather inadequate. Walterhöfer<sup>3</sup> showed that injection of epinephrine was followed by a neutrophilic leukocytosis which he attributed to the action of epinephrine on the bone marrow (cf. also Schön<sup>4</sup>). Borchardt<sup>5</sup> likewise observed leukocytosis after epinephrine, but the physiological evaluation of these experiments is doubtful since this effect occurs only after administration of large doses of epinephrine and since similar effects may be obtained also after the injection of parasympathetic stimulants such as pilocarpin and choline.

Several investigators have presented evidence that leukocytosis may follow stimulation of various parts of the central nervous system. Thus, Gotch<sup>6</sup> observed leukocytosis after injury of the corpus striatum, the thalamus and hypothalamus. Similar experiments were recently reported by Hayashida (cited after Hoff<sup>7</sup>). Injection of air into the ventricle of one partner of parabiotic rabbits was followed by a leukocytosis in the second partner suggesting that hormonal factors were involved (Beer<sup>8</sup>). Rose-now<sup>9</sup> and Foa and Roizin<sup>10</sup> likewise observed leukocytosis after stimulation of the ventricles of the brain. These findings, as well as the observation that cold (Harlow and Selye<sup>11</sup>) causes leukocytosis, are compatible with the assumption that leukocytosis is the result of an excitation of the sympathetico-adrenal system.<sup>12</sup> To prove this hypothesis, experiments were performed in which on normal and adrenodemedullated rats various procedures were employed which, according to our earlier work,<sup>13</sup> led to a stimulation of the centers of the sympathetico-adrenal system.

*Method.* The effect of convulsions induced by metrazol (50 mg. per kg. subcutaneously) and electroshock (Kessler and Gellhorn<sup>14</sup>), as well as the action of paratyphoid vaccine (Feldman and Gellhorn<sup>15</sup>), was studied on vagotomized and adrenodemedullated rats weighing 250 and 300 grams. Vagotomy was performed abdominally<sup>13</sup> in order to eliminate the vago-insulin system which is activated by these procedures together with the sympathetico-adrenal system, as our blood sugar studies indicated. Changes in blood count observed in vagotomized rats are attributable to the excitation of the sympathetico-adrenal system whereas changes occurring in adrenodemedullated rats indicate an involvement of the vago-insulin system. The food was removed 10 hours before the experiment, and blood was obtained

\* Received for publication September 7, 1943.

Aided by a grant from the Josiah Macy, Jr. Foundation.

† Present address: Univ. of Minnesota, Minneapolis, Minn.

from the tail after at least three drops had been discarded. Neubaur improved hemocytometers with standardized pipettes were used.

Following the operation at least two weeks were allowed to pass to offset the effects of the surgery and any low grade infections. Initial leukocyte counts over 25,000 were considered abnormal, in the light of the findings of previous workers (Farris<sup>10</sup>), and the animals were not used.

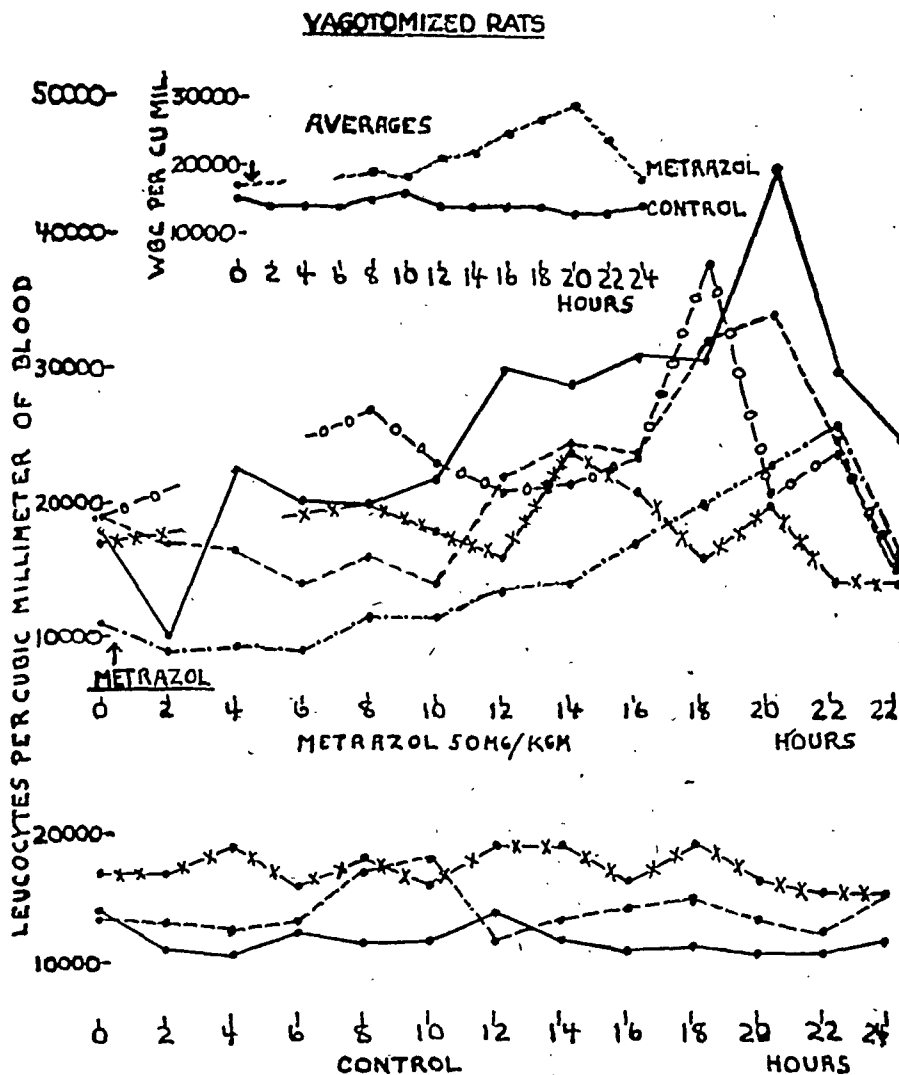


FIG. 1. Lower part. Control experiments show the variation in leukocyte count in three vagotomized rats. Samples were counted at two hour intervals for 24 hours. Middle part. Effect of metrazol convulsions (50 mg. per kg.) on the leukocyte count of vagotomized rats. Upper part. Averages of control and metrazol experiments.

Samples were taken over a 24 hour period in three vagotomized and three adrenodemedullated rats. In two of these, they were taken every hour. In the remainder they were taken every two hours.

*Results.* Bi-hourly leukocyte counts for a period of 24 hours showed only slight changes in three vagotomized and three adrenodemedullated rats

(figures 1 and 2). No significant changes in differential count were found. The erythrocyte count was decreased about 10 per cent at the end of the 24 hour period.

After the injection of metrazol leading to typical convulsions, blood counts were taken for 24 hours. In all vagotomized rats a considerable leukocytosis was observed with a maximum occurring approximately at the

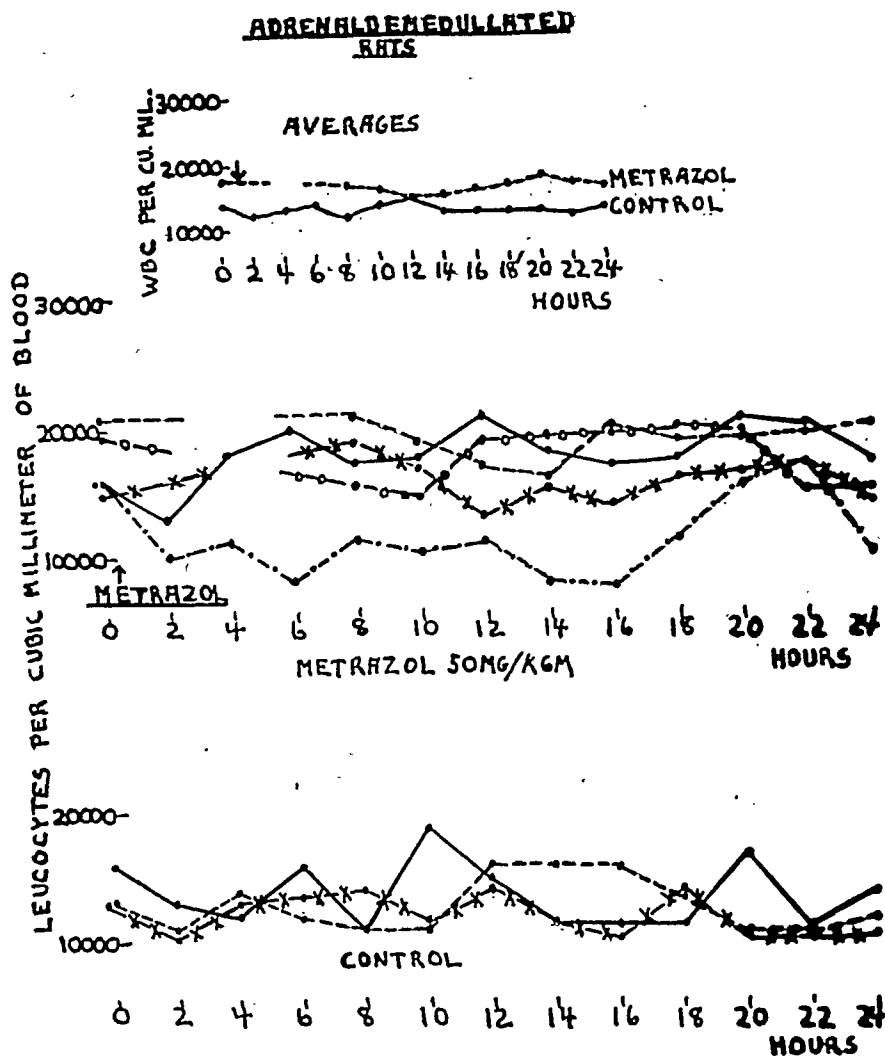


FIG. 2. Controls and metrazol effects on the leukocytes of adrenomedullated rats. Arrangement as in figure 1.

eighteenth hour, whereas the leukocytes remained unchanged in the demedullated group in spite of the fact that both groups reacted with convulsions of similar character. At the top of figures 1 and 2 are given the averages of the control and experimental groups showing that leukocytosis after metrazol convulsions is confined to the group in which the adrenal medullae are intact. The maximal increase in leukocytes in the vagotomized groups varied between 44 and 232 per cent (average 120 per cent), whereas the va-

riation in the adrenomedullated group was between 0 and 28 per cent (average 15 per cent). This increase in the number of circulating leukocytes is apparently due to a marked increase in the neutrophilic leukocytes since they showed an average increase of 100 per cent in the vagotomized group but only of 19 per cent in the adrenomedullated group.

The presence of changes in the leukocyte count in the vagotomized animals, the absence of these changes in the adrenomedullated rats, and the

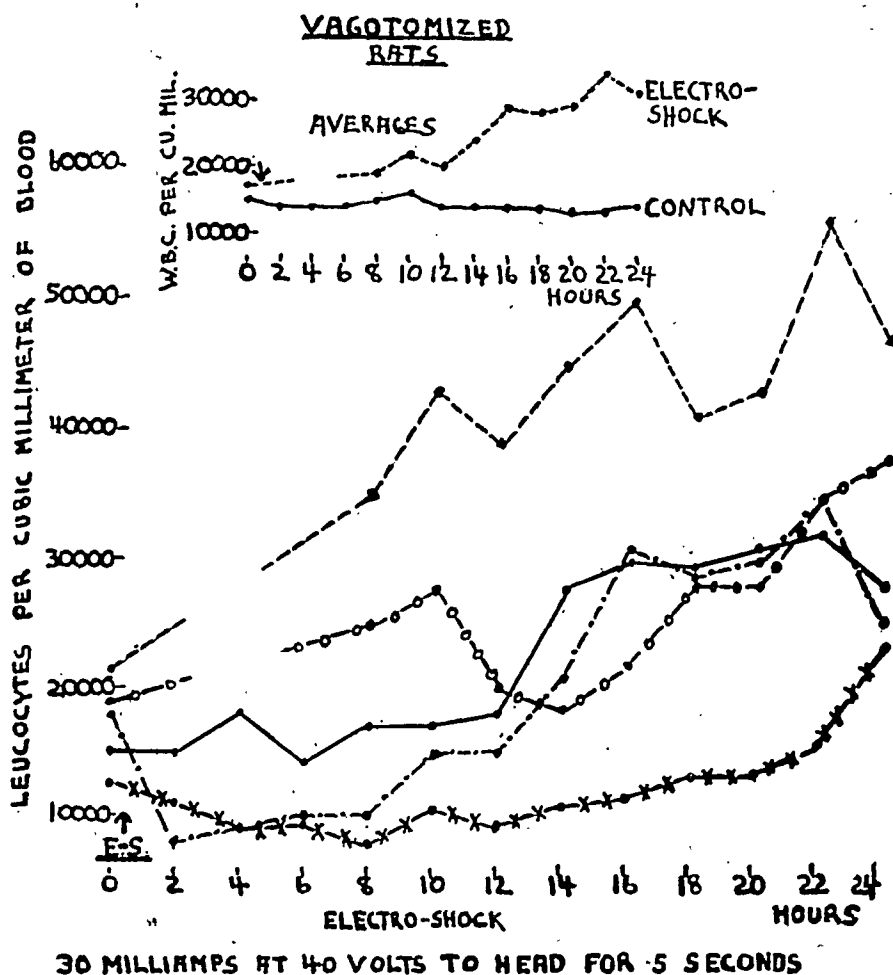


FIG. 3. Effect of electrically induced convulsions on the leukocyte count of vagotomized rats.

absence of changes in the erythrocyte count in both groups eliminate the possibility of the leukocytosis being on a concentration-dehydration basis.

The effect of electrically induced convulsions on the leukocyte count was similar to that discussed for metrazol convulsions. All the vagotomized animals showed a marked increase, whereas the adrenomedullated rats showed no significant change. This is illustrated in figures 3 and 4. The averages compared with those of similar animals under control conditions are again represented in the half-size insert graph.

The average maximal percentage increase in the leukocyte count above the initial value for vagotomized rats was 110 per cent. The adrenodemodulated rats had an average increase of only 25 per cent. Neutrophils showed on the average an increase of 50 per cent in the former and a decrease of 6 per cent in the latter.

Erythrocyte counts taken at the height of the leukocytosis showed no appreciable changes.

It is evident that the leukocytosis following metrazol and electro-shock convulsions is eliminated by adrenodemodulation.

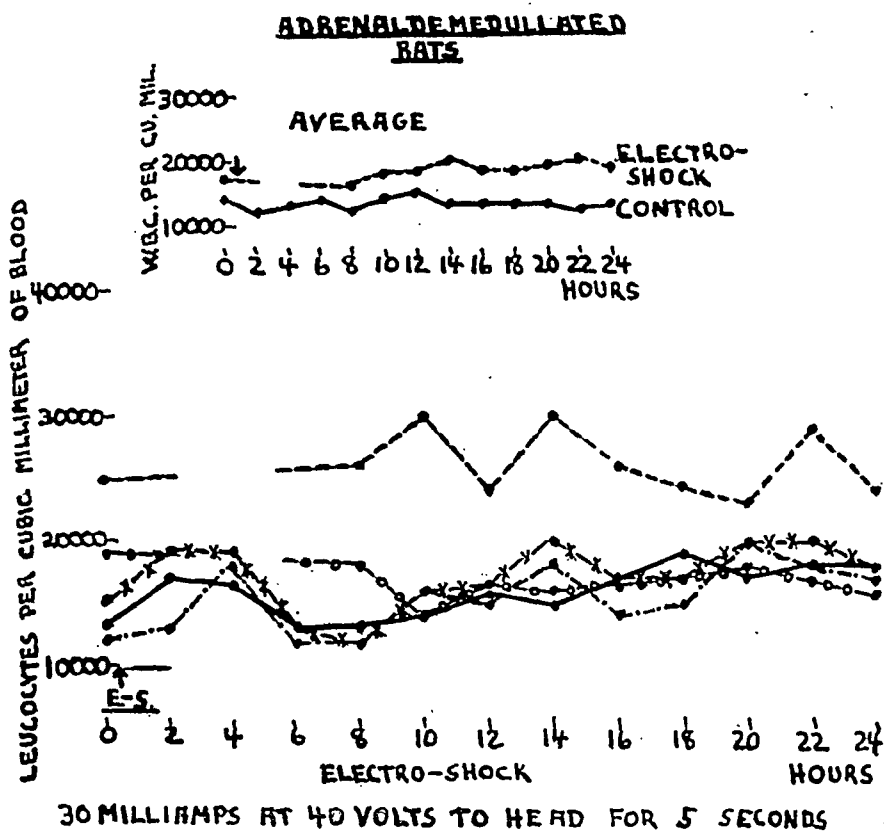


FIG. 4. Effect of electrically induced convulsions on the leukocyte count of adrenodemodulated rats.

Results of typhoid-paratyphoid vaccine injections were not so clear cut. All of the 10 rats studied, vagotomized and adrenodemodulated alike, developed a marked leukocytosis after the injections. There was a slight decrease in the erythrocytes as shown by counts taken at the beginning and end of the experiments. Differential counts suggested a leukocytosis of neutrophilic origin.

Figures 5 and 6 illustrate the individual records of these rats. In general it may be noted that the peak of the leukocytosis occurred in about 10 hours, whereas in the cases previously discussed it took place after 18 to 20 hours. Adrenodemodulation does not eliminate the leukocytosis following



typhoid-paratyphoid vaccine, although it appears to alter its characteristics. The vagotomized rats showed a steady and consistent increase followed by a return to normal whereas the curve was rather irregular in the adreno-demmedullated group.

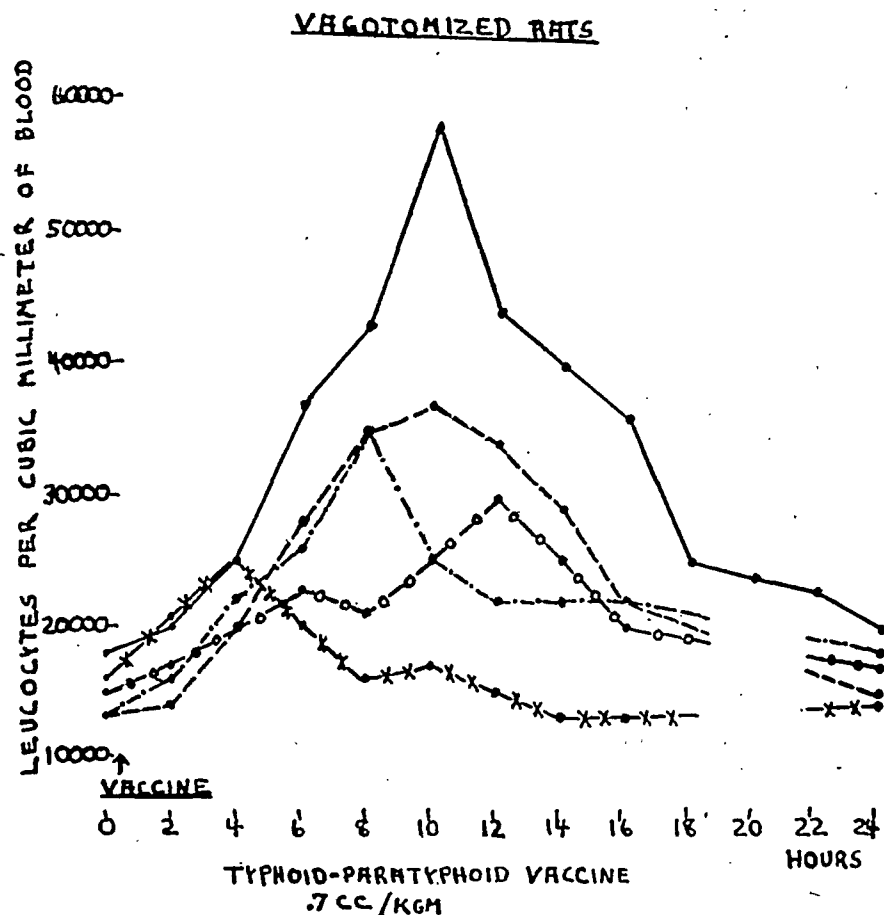


FIG. 5. Effect of typhoid-paratyphoid vaccine (.7 c.c. per kg., intraperitoneally) on the leukocyte count of vagotomized rats.

### DISCUSSION

The fact that leukocytosis occurs after electrically or chemically (metrazol) induced convulsions in the vagotomized but not in the adrenomedullated rats suggests that leukocytosis results from the liberation of adrenalin following excitation of sympathetic centers by these procedures. This interpretation is supported by previous studies which clearly showed that these convulsive procedures lead to an excitation of the sympathetico-adrenal system since the blood sugar rise is confined to the normal animals and does not occur in adrenomedullated rats.<sup>13</sup> No evidence could be found in the present series for an influence of the vago-insulin system on the blood picture.

The relatively long latent period and persistence of the leukocytosis as well as its neutrophilic character points to the bone marrow as the site of action of the liberated epinephrine. If the increase in leukocytes were due to a contraction of the spleen, it would be expected that the leukocytosis

would occur after a shorter latent period and would be of brief duration. Moreover, it would be of a lymphocytic rather than a neutrophilic character. In addition, these latter forms of leukocytosis seem to be independent of the presence of the adrenal glands.

It appears very likely that this interpretation is applicable to man. The temporary increase in leukocyte count found by Low and collaborators<sup>17</sup>

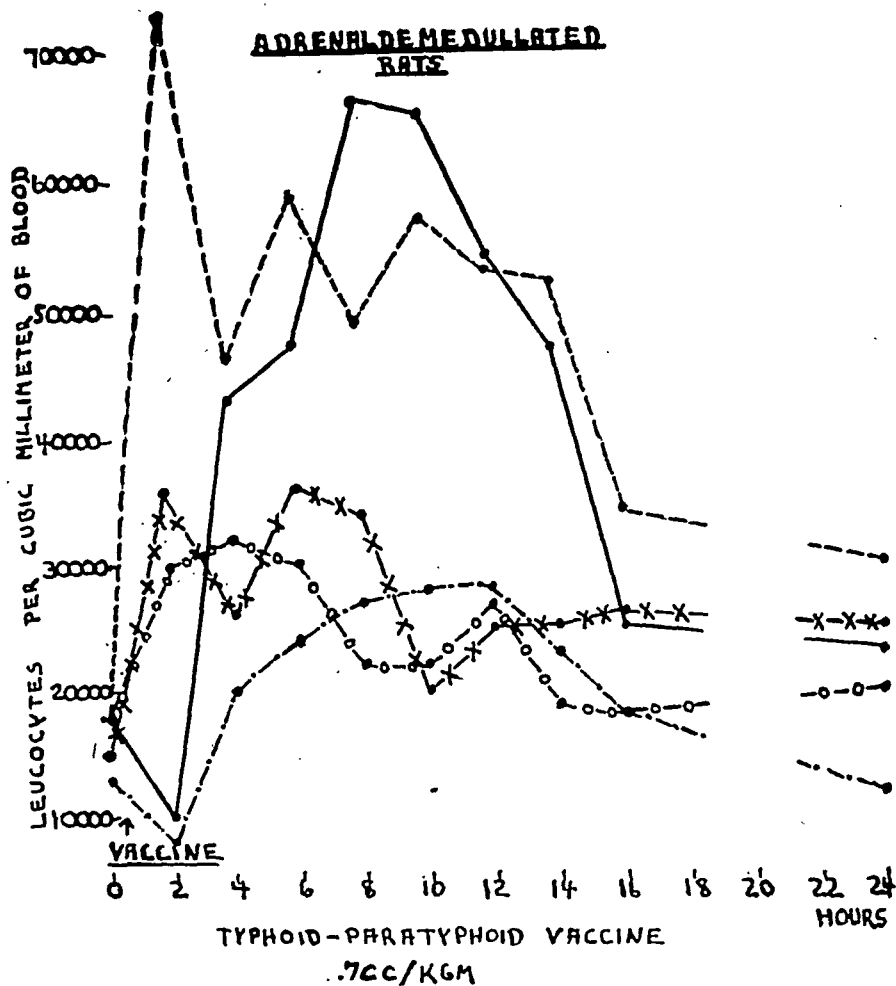


FIG. 6. Effect of typhoid-paratyphoid vaccine (.7 c.c. per kg., intraperitoneally) on the leukocyte count of adrenomedullated rats.

after metrazol convulsions is probably due to a discharge of epinephrine. The identity of these changes with those found in our animals is made even more probable by the observations of Horn,<sup>18</sup> who demonstrated a neutrophilic leukocytosis in patients after metrazol convulsions. It is of interest to note that Horn attributed this effect to a stimulation of sympathetic centers in the midbrain.

The interpretation given to our experiments on leukocytosis following metrazol injections and the application of electro-shock involves the excitation of central autonomic centers with subsequent sympathetico-adrenal discharge. If this interpretation is correct, it should be possible to prove that

other conditions leading to a sympathetico-adrenal discharge likewise induce a leukocytosis. This is indeed the case as shown by our studies on the effect of various forms of anoxia on leukocytosis.<sup>10</sup> Furthermore, our interpretation presupposes that adrenodemedullation acts only by elimination of adrenalin secretion under conditions which lead to a stimulation of the sympathetico-adrenal centers. The fact that metrazol and electro-shock fail to cause leukocytosis in adrenodemedullated rats, although this effect is regularly observed when the adrenal medulla is present, as well as the observations of Walterhofer, Reicher, Borchart, and Schon that the injection of adrenalin produces a leukocytosis, further substantiates our hypothesis.

Our interpretation is likewise applicable to the studies of Milhorat<sup>20</sup> as well as Mora and collaborators<sup>21</sup> who observed leukocytosis as a result of emotional excitement.

The preceding discussion has clearly shown that the leukocytosis following metrazol and electro-shock convulsions is due to a sympathetico-adrenal discharge. Other conditions such as anoxia and emotional excitement which lead to a sympathetico-adrenal discharge may likewise cause a leukocytosis in this manner. There are, however, complicating factors. Our experiments on typhoid-paratyphoid vaccine injections have clearly shown that the sympathetico-adrenal discharge which is well established under these conditions (Gellhorn and Feldman) is not the only factor responsible for the leukocytosis, since vagotomized and adrenodemedullated rats showed this effect to a similar degree. The leukocytosis cannot be the consequence of fever, since Feldman, Gellhorn, and Cortell<sup>15</sup> found an increase in temperature in the normal and a decrease in the adrenodemedullated animals after typhoid-paratyphoid vaccine. The results suggest that the typhoid-paratyphoid vaccine acts on the bone marrow directly, possibly in addition to the action of the vaccine on the sympathetic centers.

#### SUMMARY

The effect of metrazol and electrically induced convulsions as well as the action of typhoid-paratyphoid vaccine on the leukocyte count was studied in vagotomized and in adrenodemedullated rats. The abdominal vagotomy served to eliminate the vago-insulin system. It was found that convulsions caused by metrazol and electro-shock caused in every vagotomized rat a neutrophilic leukocytosis reaching a maximum in 18 to 24 hours and averaging 115 per cent. No leukocytosis was found in adrenodemedullated animals. It is concluded that the leukocytosis following metrazol and electro-shock convulsions is due to a sympathetico-adrenal discharge. The epinephrine secreted is believed to act on the bone marrow.

Typhoid-paratyphoid vaccine produces leukocytosis in both vagotomized and adrenodemedullated animals with a maximal effect after 10 hours. The results appear to indicate that the paratyphoid vaccine exerts some direct action on the bone marrow which is responsible for the increase in the number of leukocytes.

## BIBLIOGRAPHY

1. MÜLLER, E. F.: Evidence of nervous control of leucocytic activity by the involuntary nervous system, *Arch. Int. Med.*, 1926, xxxvii, 268-280.
2. HOFF, F.: Blut und vegetative Regulation, *Ergebn. d. inn. Med. u. Kinderh.*, 1928, xxxiii, 195-265.
3. WALTERHÖFER, G.: Die Veränderungen des weissen Blutbildes nach Adrenalininjektionen, *Deutsch. Arch. f. klin. Med.*, 1921, cxxxv, 208-223.
4. SCHÖN, R.: Über den Mechanismus der Adrenalinwirkung aufs Knochenmark, *Arch. f. exper. Path. u. Pharmakol.*, 1925, cvi, 78-88.
5. BORCHARDT, W.: Zur Physiologie des Fiebers, *Arch. f. exper. Path. u. Pharmakol.*, 1928, cxxxvii, 45-70.
6. GOTCH, HAJINE, Cited after HOFF, F.: Japanische Beiträge zum Problem der zentralnervösen Blutregulation, *Klin. Wchnschr.*, 1938, xvii, 638-640.
7. HOFF, F.: Japanische Beiträge zum Problem der zentralnervösen Blutregulation, *Klin. Wchnschr.*, 1938, xvii, 638-640.
8. BEER, A. G.: Experimentelle Untersuchungen über die Leukocytenregulation, *Klin. Wchnschr.*, 1938, xvii, 1397.
9. ROSENOW, G.: Leucocytosis induced by injection of kaolin into cisterna and ventricles of the brain, *Proc. Soc. Exper. Biol. and Med.*, 1941, xlvi, 5-9. Hirnstichleukocytose-Untersuchungen über die zentral-vegetative Blutregulation, *Ztschr. f. d. ges. exper. Med.*, 1929, lxiv, 452-461.
10. FOA, P., and ROIZIN, L.: Influenza del sistema nervoso centrale sulla composizione morfologica del sangue, *Arch. di fisiol.*, 1935, xxxv, 170-195.
11. HARLOW, C. M., and SELYE, H.: The blood picture in the alarm reaction, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 141-144.
12. GELLHORN, E. and FELDMAN, J.: The influence of cold and heat on the vago-insulin and the sympathetico-adrenal systems, *Am. Jr. Physiol.*, 1941, cxxxiii, 670-675.
13. FELDMAN, J., CORTELL, R., and GELLHORN, E.: On the vago-insulin and sympathetico-adrenal systems and their mutual relationship under conditions of central excitation induced by anoxia and convulsant drugs, *Am. Jr. Physiol.*, 1940, cxxxi, 281-289. On the vago-insulin and sympathetico-adrenal systems and their mutual relationship. II. Reaction to bulbo-capnine and cocaine, *Proc. Soc. Exper. Biol. and Med.*, 1941, xlvi, 157-160.
14. KESSLER, M., and GELLHORN, E.: The effect of electrically induced convulsions on the vago-insulin and sympathetico-adrenal system, *Proc. Soc. Exper. Biol. and Med.*, 1941, xlvi, 64-66.
15. FELDMAN, J., and GELLHORN, E.: The influence of fever on the vago-insulin and sympathetico-adrenal systems, *Endocrinology*, 1941, xxix, 141-143.
16. FARRIS, E. J., CRESKOFF, A. J., and FITZ-HUGH, T., JR.: Hematology of the rat. The Rat, 1942, J. B. Lippincott Co., Philadelphia.
17. LOW, A. A., BLAUROCK, M. F., KAPLAN, M., and SHERMAN, I.: Metrazol shock treatment of the "functional" psychoses, *Arch. Neurol. and Psychiat.*, 1938, xxxix, 717-736.
18. HORN, W.: Weisses Blutbild und Krampfbehandlung, *Psychiat.-neurol. Wchnschr.*, 1939, xli, 513-515.
19. CLARE, F. B., CRESS, C. H., and GELLHORN, E.: Effect of various forms of anoxia and of conditions causing excitation of sympathetic centers on leucocytosis, *Federation Proc.*, 1943, ii, 7.
20. MILHORAT, A. T., SMALL, S. M., and DIETHELM, O.: Leucocytosis during various emotional states, *Arch. Neurol. and Psychiat.*, 1942, xlvi, 779-792.
21. MORA, J. M., AMTMAN, L. E., and HOFFMAN, S. J.: Effect of mental and emotional states on the leucocyte count, *Jr. Am. Med. Assoc.*, 1926, lxxxvi, 945-946.

# EXTRARENAL UREMIA: REPORT OF TWO CASES DUE TO PYLORIC OBSTRUCTION\*

By EDWARD J. O'DONOVAN, M.D., and FRANCIS D. MURPHY, M.D.,  
F.A.C.P., *Milwaukee, Wisconsin*

UREMIA is an anticipated complication of nephritis, obstructions to the urinary tract, and all degenerative and inflammatory diseases of the kidneys. In the absence of these diseases, it is less commonly found and less commonly searched for. The subject of extrarenal uremia is not new. As a complication superimposed upon an already serious medical or surgical disorder, however, its importance is great and its interest paramount. Two cases of extrarenal uremia treated at the Milwaukee County Hospital are reported here.

## CASE REPORTS

*Case 1.* A 56 year old, American born, white male entered the Milwaukee County Hospital the evening of February 21, 1942. The patient was awake and quiet, but disoriented and unable adequately to voice complaints. He had been suffering from nausea and vomiting of one month's duration.

In May of 1941, he had been operated on at a hospital in another city for a peptic ulcer. He left the hospital after an uneventful postoperative course and went to work in Michigan. From there he returned to Milwaukee two days before entrance to this hospital, and complained to his wife that for the past month he had been unable to eat without vomiting shortly thereafter. Since his return home, vomiting had occurred every time an attempt was made to take food or water; for that reason, very little had been ingested during the 48 hours prior to admission to the hospital. Twenty pounds in weight had been lost. Pain had not been prominent.

On examination there was found a middle-aged, white male, only moderately well nourished, grossly confused and somewhat lethargic. The patient's temperature was slightly subnormal, and was never remarkable until the terminal rise. Blood pressure was 105 mm. Hg systolic and 85 mm. diastolic. Essential features of the physical examination were moderate dehydration, soft and doughy abdomen without marked tenderness, adequate liver dullness, depressed peristaltic sounds, a right upper quadrant, paramedian, healed, surgical scar, and the presence of normal fecal material in the rectum. The eyegrounds were examined and nothing abnormal was found. No urine was obtainable on admission.

Several thousand cubic centimeters of parenteral fluids were given, and in the morning the patient appeared slightly better for a short time. Vomiting began, however, when ingestion of water was attempted.

A program of nothing by mouth was followed, with administration of 4,000 cubic centimeters daily of parenteral fluids in the form of normal saline and 5 per cent glucose. Hydration was still inadequate, and the patient's mental condition remained confused and poorly responsive.

Chemistry of the blood 36 hours after entrance to the hospital revealed: non-protein nitrogen 226.5 mg. per 100 cubic centimeters; creatinine 4.0 mg. per 100 cubic

\* Received for publication November 1, 1943.

From the Department of Medicine, Marquette University School of Medicine, and the Medical Clinics, Milwaukee County General Hospital, Milwaukee, Wisconsin.

centimeters; chlorides 340.0 mg. per 100 cubic centimeters; carbon dioxide combining power 78.0 volumes per 100 cubic centimeters.

Parenteral fluids were increased to 5,000 cubic centimeters daily, with 2,000 of 5 per cent glucose in saline and 3,000 of plain 5 per cent glucose. Blood pressure continued within normal limits. Spinal tap revealed only a slightly increased globulin content. After 60 hours there was no evidence of free flow of urine. At this time 500 cubic centimeters were obtained by catheterization. The next day, however, a total of 850 cubic centimeters was passed spontaneously, and was described as having many white blood cells. The next day an analysis revealed clear urine.

The urinary output never reached a maximum of more than 1400 cubic centimeters in 24 hours, in spite of forced fluids. The nitrogen of the blood dropped gradually to a non-protein nitrogen value of 89 mg. per 100 cubic centimeters and creatinine of 2.3 in nine days. Administration of 5 per cent ammonium chloride by proctoclysis was followed by a rise in the blood chloride to 472 mg. per 100 cubic centimeters and a drop of the carbon dioxide combining power to 60.7 volumes per 100 cubic centimeters.

Vomiting continued, in spite of nothing by mouth. The vomited material was clear and watery. The patient's breath became foul and uremic in odor. A soft pericardial friction rub was heard on one occasion.

On the seventh hospital day, blood sodium determination was found to be 277 mg. per 100 cubic centimeters and the potassium level 20. Blood plasma was given intravenously on this day and again two days later. The temperature began to rise about this time to a level of 102° F. rectally. Pneumonia was discovered the next day, and on this, the eleventh hospital day, the patient quietly died.

A report was obtained of the patient's illness of May 1941. Operation was done at that time for a ruptured duodenal ulcer, and recovery occurred after a relatively uneventful postoperative course. Urinalysis at that time revealed a straw colored fluid without albumin or sugar.

Postmortem examination by the Pathology Department of the Milwaukee County Hospital disclosed the following important findings: 1. *Gastric* ulcer with beginning malignant degeneration. 2. Fibrous, *almost imperforate*, pyloric stenosis. 3. Interstitial renal edema and tubular degeneration. 4. Terminal bronchopneumonia.

*Case 2.* A 52 year old white laborer, who appeared irrational, restless, dyspneic and dehydrated, was admitted to the hospital. He had vomited two or three times a day for the past five months and had lost 25 pounds during that time.

The patient had entered this hospital 10 months previously when a diagnosis of perforated peptic ulcer was made. A subdiaphragmatic abscess was drained, and after recovery, the patient was advised to have an operation for the ulcer. However, he refused this suggestion. In addition to these disorders, the patient stated that he had a congenital kidney condition which had caused symptoms for most of his life. Urinalysis revealed a 3 plus albumin, and many white blood cells. Red cells and casts were absent.

On the present admission the patient was emaciated and irrational. There was constant muscular twitching, but no convulsions. There was carpopedal spasm and a positive Trousseau sign. The head was essentially negative, but the mouth and tongue were dehydrated and blood clots were found in the right nostril. Chvostek's sign was positive. There was voluntary rigidity of the neck, but it was otherwise negative. No chest abnormalities were noted. The heart was normal with a rate of 96 beats per minute. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. The abdomen was scaphoid, with a two inch scar on the right medial costal margin. Rigidity of the abdominal muscles was present. No masses were palpable and the intestinal gurgles were hypoactive. Rectal examination was negative.

Urinalysis was negative except for the abnormalities noted before, namely a 3 plus albumin and numerous white blood cells. A blood count taken 24 hours after admission showed hemoconcentration and a leukocytosis of 17,000. The initial chemical studies of the blood indicated a marked azotemia and alkalosis with hypochloremia. The accompanying table gives a detailed report on the chemistry of the

Blood Chemical Changes before Operation in Case 2

	1st Hospital Day	2nd Hospital Day	3rd Hospital Day	4th Hospital Day
Nonprotein Nitrogen	96.7 mg. %	103 mg. %	66.6 mg. %	35.9 mg. %
Urea Nitrogen	50 mg. %	49.6 mg. %		
Creatinine	3.6 mg. %	3.4 mg. %	2.5 mg. %	1.5 mg. %
Sodium Chloride	240 mg. %	420 mg. %	480 mg. %	460 mg. %
Alkali Reserve	87 vol. %	69.2 vol. %	56 vol. %	
Uric Acid	7 mg. %	5.7 mg. %		3.1 mg. %
Total Protein	9.06 Gm. %	6.8 Gm. %	5.04 Gm. %	7.41 Gm. %
Albumin	5.9 Gm. %	5.0 Gm. %	3.7 Gm. %	4.65 Gm. %
Globulin	3.16 Gm. %	1.8 Gm. %	1.34 Gm. %	2.76 Gm. %

blood during the preoperative period. There was complete gastric retention at the end of four hours. Wangenstein suction was kept in operation from the fourth to the seventh hospital days. The clinical impression was peptic ulcer with cicatrization and pyloric obstruction with alkalosis and extrarenal uremia.

Four to 6 liters of normal saline were given parenterally every day for five days. On the ninth hospital day the chemical studies of the blood showed normal figures. On the tenth hospital day the patient was operated upon. Dense adhesions were found about the pylorus, liver, and duodenum. Posterior gastroenterostomy was done, but no attempt was made to resect the pyloric end of the stomach. The patient made an uneventful recovery and left the hospital on the thirty-first postoperative day on an ambulatory ulcer diet.

### DISCUSSION

Extrarenal uremia is a clinical state characterized by elevation of the blood nitrogen, dehydration due to loss of extracellular fluid and electrolytes, normal or low blood pressure, and oliguria which may progress to anuria. The primary responsible factors are extrarenal in origin. In the cases in which death occurs, structural changes in the kidney are either entirely absent or are of insufficient degree to account for failure of renal function. By definition are excluded from classification as causes of extrarenal uremia all infections or inflammatory renal diseases, tumors, strictures, anatomical variations or other obstructions at any place in the urinary tract, nervous imbalance or paralyses which prevent the normal excretion of urine, as well as serious damage to the parenchyma of the kidney from any cause.

The diseases in which a significant degree of retention of nitrogen in the blood has been found to occur most frequently are those in which dehydration is a prominent feature. Such dehydration may be caused most notably by excessive diarrhea, vomiting, insufficient intake of water, and diabetic acidosis. Nitrogen retention following massive bleeding into the gastrointestinal tract is due in part at least to digestion and absorption of blood protein.

Dehydration is induced by abnormal loss of extracellular electrolytes and water through the avenues of vomiting, diarrhea, diuresis, sweating or through a fistulous tract. In dehydration, the evidence of loss of fluid volume is confined chiefly to extracellular fluid. Extracellular fluid is characterized by its high content of sodium, chloride and bicarbonate, and small amounts of potassium, phosphate and magnesium. The patient discussed in case 1 had a low blood sodium value and a normal blood potassium value. Blood plasma, lymph, interstitial fluid and cerebrospinal fluid represent the chief sources of extracellular fluid in the body. Gastric juice, bile and the intestinal secretions are modified forms of extracellular fluid. Sweat and urine are also modified forms of extracellular fluid which are lost to the body normally within certain limits.

Cellular membranes separate the two components containing the extracellular and the intracellular fluid. Water is free to move between the two in response to osmotic forces. The effective osmotic pressure of these two components is due largely to concentrations of sodium and potassium respectively. The distribution of these two elements is a very important, if not the chief factor, in controlling the distribution of body water.

It has been suggested that the extrarenal uremia which supervenes upon high intestinal obstruction is due to hypochloremia. The error of this conception seems now to be clearly established, although depletion of blood chlorides may occur simultaneously. The error has been revealed by the production of hypochloremia in dogs through gastric lavage or vomiting, with, however, provision for sufficient food and water for the animals. No increase in non-protein nitrogen occurred in the blood until immediately before death, although the chloride content of the blood had fallen to half its normal level.

Prolonged dehydration resulting from upper intestinal obstruction has been shown to produce definite impairment of renal function in dogs and in man, as indicated by the excretion of both urea and phenolsulfonphthalein.

Disturbance of the circulation seems to be present without exception in extrarenal azotemia. In those cases with a salt deficiency, such as follows excessive vomiting, deterioration of the circulation is induced by dehydration. Loss of sodium leads to loss of water, and the latter takes place always at the expense of extracellular fluid. Consequently the amount of circulating blood diminishes and the blood becomes more concentrated. Owing to the reduced blood volume the circulation slows down, the blood pressure may fall, and the concentration of the serum involves increase of the colloid osmotic pressure of the blood. The decrease of the blood pressure and the increase of the colloid osmotic pressure together result in diminution of filtration pressure, the extent of which in severe cases can be so great that the pressure ceases to exist at all. Diminution of the blood flow is a further factor largely inhibiting glomerular filtration.



Deterioration of the circulation is significant not only from the point of view of renal function but from that of insufficient filling of the coronary arteries as well. Characteristic electrocardiographic changes in the ST segment, voltage and T waves, at times reversible, have been reported.

There is undoubtedly increased protein disintegration in states of azotemia induced by vomiting. This is not by itself sufficient to lead to lethal azotemia, however, because there are conditions, for example the infectious diseases, in which rather severe protein disintegration takes place but lethal azotemia does not follow as long as renal function is unimpaired.

In azotemia following hemorrhage the loss of blood leads to hemodynamic changes similar to those described. In congestive heart failure the slackened blood supply of the kidneys is due to diminution of cardiac output or to passive congestion. Excessive postoperative use of pitressin by its antidiuretic effect is said to contribute to nitrogen retention.

The presence of albumin and casts in urine does not necessarily indicate an irreparable kidney lesion. These urinary findings are frequent in cases of extrarenal uremia, and their disappearance usually coincides with the return of normal urinary flow and the fall in the level of blood nitrogen to normal.

Treatment of extrarenal uremia involves replacement of water, sodium and chloride, maintenance of the normal circulation and volume of the blood, and removal of the cause of the catastrophe. Shock if present must be combated and blood transfusion probably will be valuable. Restoration of extracellular electrolytes and water is accomplished by subcutaneous or intravenous infusions of sodium chloride or one of its modifications. Seven thousand cubic centimeters daily may be required. Where acidosis is present, adjustment of acid base equilibrium may be accomplished better by intravenous sodium lactate. For alkalosis the reduction of bicarbonate of the blood by oral or parenteral ammonium chloride, by intravenous administration of dilute hydrochloric acid, or simply by salt in the form of intravenous saline or hypertonic sodium chloride solution have all been recommended. Intravenous amino acids and blood plasma have been advised for hypoproteinemia. If food is tolerated, small feedings should be given every two hours consisting of 150 to 200 cubic centimeters of concentrated liquid or semi-solid carbohydrate food. Antispasmodics of the belladonna group are often of value in full therapeutic dosage. If nausea and vomiting are present, nothing should be given by mouth. Food which is regurgitated not only accomplishes no good, but actually does harm by increasing the loss of electrolytes in the gastric secretions. The same unfavorable result may be brought about by food when it aggravates severe diarrhea. When pyloric stenosis is present, the stomach should be aspirated at least once daily. Successful termination of azotemia which had been induced by pyloric obstruction of the type described has been brought about by gastrojejunostomy, which is favorably reported and recommended. Feeding of the patient through a jejunostomy prior to the gastrojejunostomy is recommended for

selected cases where uremia does not respond to parenteral fluids' adequately for major surgical intervention.

### SUMMARY

Two cases of extrarenal uremia due to pyloric obstruction following long standing peptic ulcer are reported. One case recovered following operation, and the other died. At autopsy only insignificant renal damage, not sufficient to account for the uremia was seen. Beginning malignant degeneration was found in the ulcer area. A discussion of extrarenal uremia is given, and the etiology and importance of uremia of this type are stressed. Treatment is outlined.

### BIBLIOGRAPHY

- ALEXANDER, A. A.: Uremia of circulatory failure, *Calif. and West. Med.*, 1936, xlv, 391-395.
- BOOKLESS, A. S.: Uremia after hemorrhage (in peptic ulcer and pyloric carcinoma), *Guy's Hosp. Rep.*, 1938, lxxxviii, 22-23.
- BROWN, G. E., EUSTERMAN, G. B., HARTMAN, H. R., and ROWNTREE, L. G.: Toxic nephritis in pyloric and duodenal obstruction, *Arch. Int. Med.*, 1923, xxxii, 425-455.
- CHRISTIANSEN, T.: Uremia as cause of death in massive hemorrhage from peptic ulcer, *Acta med. Scandinav.*, 1935, lxxxv, 333-345.
- DEROW, H. A.: Significance of postoperative rises of blood nonprotein nitrogen, *New England Jr. Med.*, 1935, ccxii, 509-511.
- EVANS, T. S.: Azotemia with normal kidneys found at postmortem, *Arch. Int. Med.*, 1931, xlviii, 1231-1236.
- FALCONER, M. A., and LYALL, A.: Treatment of uremic intoxication complicating pyloric stenosis with vomiting, with report of two cases successfully treated by jejunostomy, *Australian and New Zealand Jr. Surg.*, 1938, viii, 37-56.
- GARIEPY, L. H., and GRATTON, A.: Nondiabetic coma in diabetes mellitus; case due to uremia, *Union méd. du Canada*, 1935, lxiv, 385-388.
- GARIS, R. W.: Prerenal uremia due to papilloma of rectum, *Ann. Int. Med.*, 1941, xv, 916-926.
- GOMORI, P., and FRENREISZ, S.: Osmoregulation disturbance of tissues in "hypochloremic" azotemia, *Acta med. Scandinav.*, 1937, xcii, 497-502.
- GOMORI, P., and FRENREISZ, S.: Influencing "hypochloremic" azotemias with hypertonic and physiological salt solution, *Acta med. Scandinav.*, 1937, xcii, 503-514.
- GOMORI, P., and PODHRADSKY, L.: Protein disintegration in "hypochloremic" azotemia after pylorus obstruction and its mechanism, *Acta med. Scandinav.*, 1937, xcii, 515-524.
- GOMORI, P., and PODHRADSKY, L., and KRING, J.: Significance of circulation in the pathogenesis of extrarenal azotemia, *Acta med. Scandinav.*, 1939, cii, 591-610.
- GOMORI, P., and VON GRUBER, Z.: Coronary insufficiency in extrarenal azotemia, *Klin. Wchnschr.*, 1939, xviii, 1417-1421.
- LAYNE, J. A., and MOIR, W. W., JR.: Extrarenal uremia, *Internat. Clin.*, 1941, iv, 182-203.
- LEMIERRE, A., LAUDAT, M., and MEYER, A.: Azotemia developing after prolonged vomiting; chlorides of blood and urine; etiologic, diagnostic and therapeutic study of case, *Bull. et mém. Soc. med. d. Hôp. de Paris*, 1936, lii, 491-500.
- MADDOCK, W. G., and COLLIER, F. A.: Water balance in surgery, *Jr. Am. Med. Assoc.*, 1937, cviii, 1-7.

MEYLER, L.: Uremia due to dehydration, *Acta med. Scandinav.*, 1936, xc, 475-488.

MOIR, W. W., JR., and LAYNE, J. A.: Extrarenal uremia, *Minnesota Staff Meet. Bull.* April 19, 1940, xi, no. 23.

MOUSSEAU, J. A.: Extensive pyloric stenosis of ulcerous origin with azotemia due to lack of chlorides: recovery of case after surgical treatment, *Union méd. du Canada*, 1937, lxvi, 834-840.

RACHMILEWITZ, M.: Acute extrarenal azotemia, *Lancet*, 1934, i, 78-81.

REINWEIN, H.: Extrarenal azotemia, *Med. Klin.*, 1939, xxxv, 1336; 1368; 1393.

# CASE REPORTS

---

## CHYLOTHORAX; BRIEF REVIEW OF LITERATURE; REPORT OF THREE NON-TRAUMATIC CASES \*

By WILLIAM E. JAHSMAN, M.D., F.A.C.P., *Detroit, Michigan*

CHYLOTHORAX, an effusion of chyle in the pleural cavity, holds our interest because it is a relatively rare condition, may be of obscure etiology and may have unusual pathologic lesions. According to Brescia,<sup>1</sup> Bartolet first described this entity in 1633, and Quincke<sup>2</sup> reported the first authoritative case in 1875. Yet, 56 years later, in 1931, Van Nuys<sup>3</sup> was able to collect but 66 cases of chylothorax of all types, and according to Nowak and Barton,<sup>4</sup> only 84 cases were reported up to 1937. Høyer,<sup>5</sup> who says it is an exceedingly rare condition, found no additional cases up to 1938 when he reported the eighty-fifth case, the first from Norway.

Since that date we have found reported in English 11 additional single cases by different authors: namely, Harrell, Street and Reiser,<sup>6</sup> and Everhart and Jacobs<sup>7</sup> in 1939; Gordon,<sup>8</sup> Cookson and Slade,<sup>9</sup> Cellan-Jones and Murphy<sup>10</sup> and Matson and Stacy<sup>11</sup> in 1940; Sullivan,<sup>12</sup> Brescia,<sup>1</sup> Nowak and Barton,<sup>4</sup> and Smith and Woliver<sup>13</sup> in 1941; and Dorsey and Morris<sup>14</sup> in 1942. Six other single cases are reported in foreign journals not available for review. The authors are as follows: Douady, Dupuy and Bouvrain<sup>15</sup>; Fujita, Bando and Sugishita<sup>16</sup>; Cercas<sup>17</sup>; Cziglány<sup>18</sup>; Lamartine de Assis and Raino<sup>19</sup>; and Foffani.<sup>20</sup> Adding these last six brings the total reported cases of chylothorax, at the present writing, to 102. To this group I wish to add three cases observed at the Henry Ford Hospital, none with associated trauma, making the total to date 105.

### CASE REPORTS

*Case 1.* F. B., a white male, age 54, was first seen on March 6, 1939 because of swelling of the left arm and left side of the neck of six months' duration. Positive findings included a large, hard thyroid gland, possibly malignant; enlarged left anterior cervical and submaxillary glands; lymphedema of left arm and left cervical and upper chest regions; flat percussion note over the left lower chest; blood pressure 150 mm. Hg systolic and 90 mm. diastolic; and slightly enlarged prostate gland believed to be benign.

There was a history suggestive of coronary occlusion three years before this illness, but no confirmative evidence in the electrocardiographic tracing taken at this admission. There *was* evidence of arteriosclerotic heart disease.

Roentgenograms of the chest gave evidence of a collection of fluid in the left pleural cavity, but no mediastinal mass. There was slight widening of the upper mediastinum and the trachea was displaced slightly to the right.

\* Received for publication September 1, 1942.

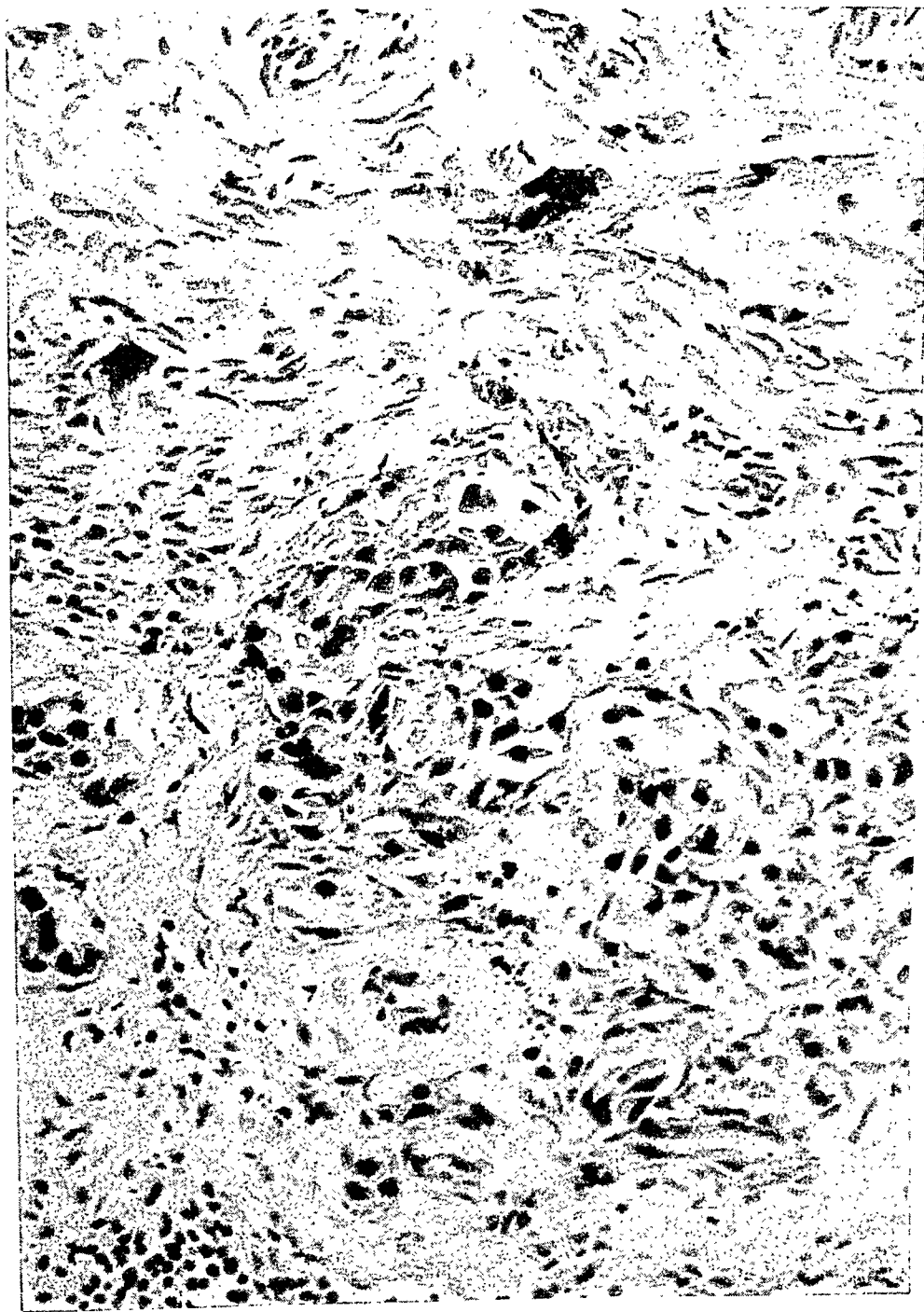


FIG. 1. Photomicrograph of section taken from cervical lymph gland of case 1. Lymphoid structure almost completely replaced by metastatic tumor growth, which is composed of small polyhedral epithelial cells arranged in atypical alveoli and in small solid masses and groups. Occasional mitotic nuclei present. Hematoxylin and eosin stain.

Aspirated pleural fluid was milky, sterile. It contained much fat and 950 mg. of protein per 100 c.c., and had a specific gravity of 1.014, thus meeting most of the criteria for true chylous fluid.

Biopsy of a neck gland was reported by the pathologist as metastatic carcinoma. A photomicrograph of the section of the gland is shown in figure 1.

Roentgen-ray therapy was given in small doses daily for several days. The patient seemed about as usual after his treatment on the twelfth day. He had talked with his nurse at 11:45 a.m. and at 12:20 p.m. was found dead in his chair.

At autopsy there was a fresh occlusion of the coronary artery at the site of advanced sclerotic changes. There was also evidence in the heart of previous myocardial infarction. Abdominal and pelvic lymph nodes, as well as mediastinal and cervical, were involved with metastatic carcinoma. There was a small area in the prostate gland suspicious in the gross of being malignant, and microscopic examination showed adenocarcinoma Type III.

*Case 2.* W. G., a white man, aged 64, first came for examination on March 14, 1940 because of dyspnea, anorexia and "gas" after meals, causing "pressure on the heart." There was some substernal distress on exertion, cough at times, and swelling of the ankles late in the day. He had lost 17 pounds in two months.

Findings: Weight still 20 pounds above ideal; some respiratory distress; flat percussion note over the left lower chest; a few moist râles at the right base; and mild pitting edema of the ankles.

The cardiologist felt that the symptoms and findings could be adequately explained by heart failure.

Roentgenograms of the chest showed moderate enlargement of the heart and aortic shadows. The hilus areas were considerably accentuated. There was marked increase in the bronchovascular markings throughout both lungs and evidence of some fluid in the left pleural cavity. There was a small area of pneumothorax at the left apex.

Pleural fluid was aspirated four times in 12 days, 1600 c.c. each time. It was turbid, not milky, but the specific gravity ranged from 1.017 to 1.021, the fluid contained much finely emulsified fat and had a high protein content. Pathological report of the fluid was "pleural exudate—no tumor cells."

Gastrointestinal examination revealed only chronic gastritis. An electrocardiographic tracing taken after the third pleural fluid aspiration showed sinus tachycardia, inverted T-waves in Leads I, II and III, but a normal Lead IV.

There was rapid reaccumulation of pleural fluid, later on both sides, and without other findings of cardiac failure. The fluid soon became creamy and remained so after April 23, 1940. Twenty-two aspirations were done up to September 10, 1940, with removal of a total of 42,900 c.c. of fluid. During this time there was progressive weight loss and emaciation. Because of the inconvenience and difficulty of returning to the hospital frequently, the patient was cared for at his home by the family physician after September 10, 1940. He died in December, 1940. There was no post-mortem examination, but the family physician's clinical impression corresponded with that of our staff, namely, obstruction of the thoracic duct due to malignancy.

*Case 3.* F. C., a white woman, aged 63, was first seen at the hospital on December 20, 1941 because of pain in the right upper arm and shoulder of six months' duration. A lump had appeared on the left side of the neck in October, 1941, and, though painless, had steadily increased in size. Roentgenograms of the chest at that time had shown a mediastinal mass. This and the neck swelling had decreased in size with roentgen-ray therapy. Dyspnea followed and was relieved by aspiration of pleural fluid by the family physician.

Positive findings on admission to the hospital included: evident weight loss; pallor; weakness; several enlarged cervical lymph glands; flat percussion note over the lower half of the chest; and enlarged liver.

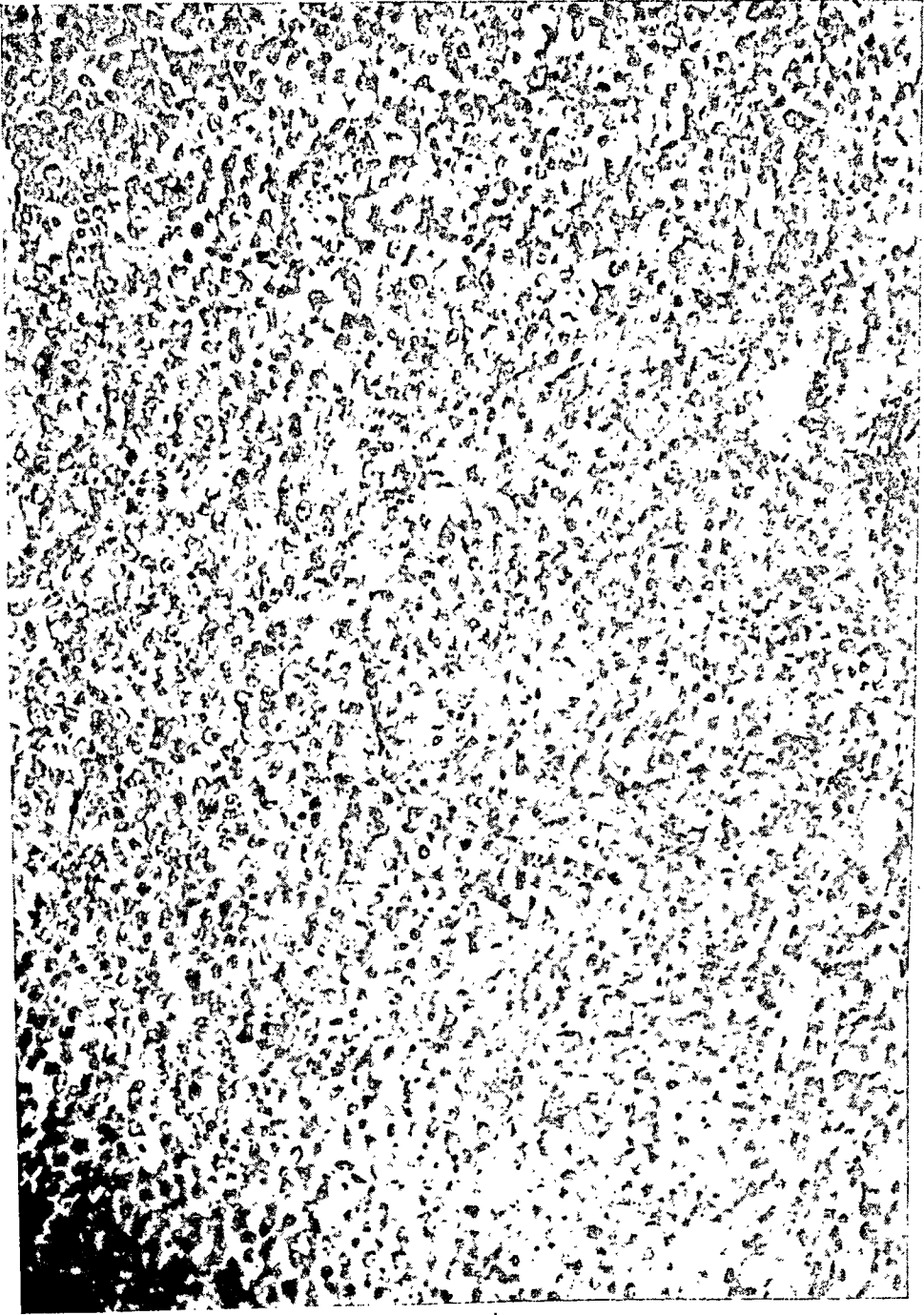
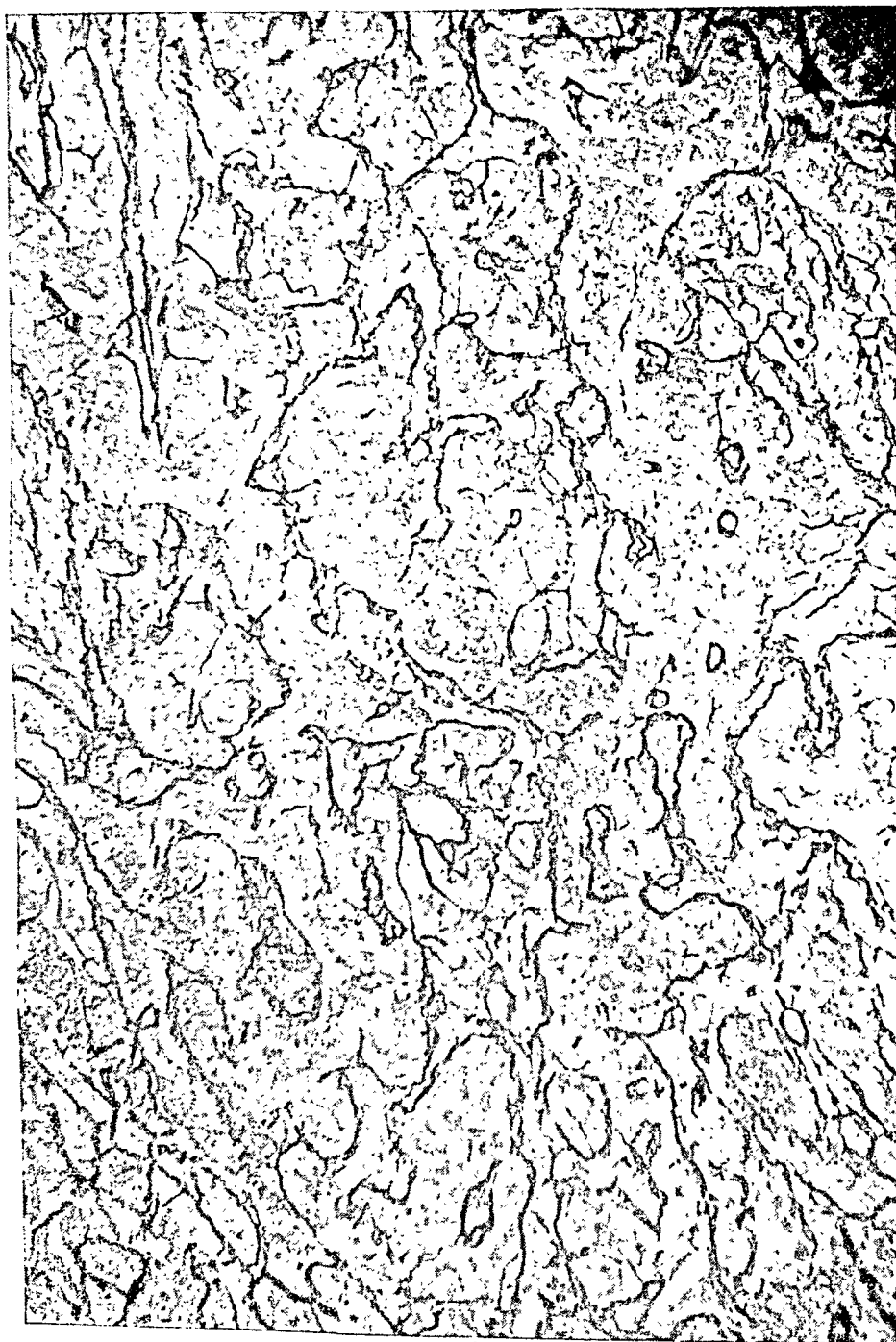


FIG. 2. Photomicrographs of section through cervical lymph node of case 2, showing complete destruction of architectural pattern. There are closely packed, large, irregular tumor cells with abundant cytoplasm and elongated branching processes. Nuclei are hyperchromatic and contain numerous mitotic figures. A. Hematoxylin and eosin stain. B. Special reticulum stain.



B



Roentgenograms of the chest showed suggestive widening of the mediastinum just below the clavicles, possibly due to glandular enlargement; fluid in both pleural cavities; and slight pneumothorax at the right apex.

Pathological report of biopsy of a cervical gland was "lymphoblastoma, reticulum-cell sarcoma type." A photomicrograph of this tissue is shown in figure 2.

Pleural fluid was milky, and, on standing, a creamy top layer formed. There was practically no odor. Specific gravity was 1.013. Fat was present in large quantity and could be easily seen microscopically. The protein content was 3.8 grams per 100 c.c. of fluid. Culture of the fluid was negative. It was unquestionably chylous fluid, reaccumulating rapidly and showing the same characteristics each time that it was aspirated. A total of 6500 c.c. was removed in five aspirations.

The patient responded very poorly to roentgen-ray and symptomatic therapy, became progressively weaker and more emaciated, and died February 5, 1942.

The autopsy report is as follows: "Lymphoblastoma, reticulum-cell sarcoma type, involving the entire lymphoid system, epicardium, liver, lungs, pleura, kidneys and pericardial tissues; early lobar pneumonia; pulmonary fibrosis; fibrinous pleuritis; bilateral chylothorax; aortic atherosclerosis; mild arteriosclerotic disease of kidneys."

#### COMMENT

The appearance of chylous fluid in one or the other pleural cavity seems to bear some relation to the location of the perforation in or obstruction to the thoracic duct in its anatomical course. The latter has been ably reviewed by Gordon<sup>8</sup> and Brescia,<sup>1</sup> and will not be discussed here. However, it would seem that injuries or obstruction to the duct lower down would account for effusion presenting itself on the right side, whereas those higher up would produce effusion on the left. Because of anomalies of the duct or extensive involvement as from trauma or new growth, there are exceptions, as illustrated by Heppner's case.<sup>21</sup>

#### ETIOLOGY

Chylous fluid in the pleural cavity results from any condition that interferes with the normal flow of chyle through the thoracic duct, either from a break in the duct or obstruction to it. Revising and enlarging upon the causes given by McNabb and Scarlett,<sup>22</sup> I would summarize the etiological factors as follows:

- I. Destructive damage to the thoracic duct or its terminals.
  1. Trauma to the chest without fracture of bone.
  2. Trauma to the chest with fractured ribs, clavicle or vertebrae.
  3. Duct accidentally severed at operation.
  4. One or more terminals severed.
  5. Gunshot or stab wounds.
  6. Perforating lymphangitis involving duct or terminals.
  7. Aneurysm of duct with rupture.
- II. Obstruction to the thoracic duct.
  1. Within the duct or terminals.
    - a. New growth.
    - b. Filaria.

2. From outside the duct.

- a. New growths and granulomata; carcinoma, lymphosarcoma, tuberculous glands.
- b. Thrombosis of left subclavian vein.
- c. Cirrhosis of liver.

III. Spontaneous or of unknown origin.

The spontaneous type occurs in infants under one year of age in whom a congenital defect or weakness of the duct must be strongly considered. In seven of 10 infants under one year of age reviewed by Brescia,<sup>1</sup> the cause for chylothorax was given as spontaneous.

Trauma is by far the largest single cause. Though Shackelford and Fisher<sup>23</sup> succeeded in tracing only 41 authentic traumatic cases to which they added two of their own in 1938, Høyer<sup>5</sup> in the same year reported 48 out of a total of 84 from all causes, and, of the eleven other reported cases we have added, eight were traumatic.

Various types of trauma are described. Crushing injuries to the chest are the most common according to Shackelford and Fisher.<sup>23</sup> One of the earliest cases due to chest injury was reported by Finkelstein<sup>24</sup> in 1901. Final rupture of the duct occurred with a severe cough that developed after a latent period of a month. Another with a still longer latent interval was reported by Beatty,<sup>25</sup> actual symptoms of chylothorax developing six and one half years after an automobile accident. Straus<sup>26</sup> describes a case due to a bullet wound of the thoracic duct, one of the rarer traumatic causes.

Two of the cases reported in this paper were due to new growth outside the thoracic duct and the third was thought due to malignancy also, though this was not established by actual pathological diagnosis or by autopsy. In adults, this, namely malignancy, is the second most common cause of chylothorax.

### DIAGNOSIS

This is dependent on thoracentesis and careful examination of the fluid. The chief characteristics of chylous fluid according to Gaudin,<sup>27</sup> Nowak and Barton,<sup>4</sup> and Wallis and Scholberg<sup>28</sup> are the following:

1. Milky appearance.
2. Generally shows distinct creamy layer on standing.
3. Finely emulsified, with fine fat globules.
4. No odor or odor corresponding to odor of food eaten.
5. Reaction alkaline.
6. Specific gravity generally exceeds 1.012.
7. Degree of opalescence more or less constant.
8. Sterile and resists putrefaction.
9. Fat content generally high, 0.4 to 4 per cent, and like fat in food.
10. Total solids usually greater than 4 per cent.
11. Total protein generally exceeds 3 grams per 100 c.c.
12. Salts and organic substances approximate the values found for chyle from the thoracic duct.

The fluid may also be examined microscopically for fat droplets. In traumatic cases, Lillie and Fox<sup>20</sup> mention as aids in diagnosis such striking clinical features as:

1. The latent period before onset of symptoms (it takes time for the fluid to penetrate the pleural wall).
2. Rapid reaccumulation of fluid within the chest after aspiration.
3. The gradual progressive emaciation which frequently ends in death.

In addition to the features mentioned, Mouchet<sup>30</sup> observed:

1. Collapse or shock, caused by change in intrathoracic pressure.
2. Inanition, oliguria, and thirst, probably from breakdown of lipid metabolism or loss of some unknown hormone or enzyme.

### PROGNOSIS

The outlook in most of these cases is usually grave. The reported mortality in traumatic chylothorax is approximately 50 per cent, in spite of various methods of therapy, and in the cases due to new growth, the outcome is invariably fatal. The loss of fluid so rich in protein and fat as chyle quickly leads to dehydration and malnutrition if not replaced by various forms of therapy.

### TREATMENT

Smith and Woliver<sup>18</sup> feel that the therapy of chylothorax must satisfy several requirements, namely prevention of the loss of chyle, maintenance of nutrition and prevention of infection in the chest. This means essentially, then, aspiration and, if possible, intravenous reinfusion of the aspirated fluid, as was attempted by Oeken<sup>31</sup> and later done by Bauersfeld.<sup>32</sup> The fluid aspirated may be stored in the ice box and then given intravenously as desired, first being sure it is sterile by culture. Aspirations should be done only as necessary to relieve respiratory distress, since the increased pressure of fluid may help to close a fistula. Some writers recommended a low fat diet to decrease the flow of chyle.

Smith and Woliver<sup>18</sup> feel that early operation for traumatized ducts is not advisable because of the usual inaccessibility of the duct or the poor condition of the patient. Besides, these tears often heal or close spontaneously. These authors feel that open external drainage of chyle should be avoided unless empyema supervenes. Yet, most writers are agreed that surgery has a place, such as correction of deformity from fracture of a clavicle causing pressure, or suture of a ruptured duct in the supraclavicular portion. Nowak and Barton<sup>4</sup> cured their case by phrenicotomy, the stoma apparently being walled off by the resultant elevation of the diaphragm. They suggest phrenicotomy or phrenic nerve crushing if repeated aspiration and intravenous reinfusion fail to produce adequate response. And Brown<sup>33</sup> feels that in those cases with a rather long latent period and an early stage of effusion, termed "retropleural chyloma," early thoracotomy and extrapleural drainage should be done with the object of preventing rupture or diffusion into the pleural space. Selection of cases for surgery is important.

## SUMMARY

1. The relative rarity of chylothorax is emphasized by the fact that up to the time of this report only 102 cases could be collected from the literature. There are probably others not recognized or reported.

2. Traumatic cases predominate but those due to new growths outside the thoracic duct are not uncommon. Two of the cases here reported and probably the third were due to new growth outside the duct.

3. Diagnosis is dependent primarily on aspiration and identification of chylous fluid.

4. Treatment consists essentially of aspiration of fluid as necessary to relieve respiratory distress, and intravenous reinfusion of the fluid to prevent rapid emaciation. In selected cases surgery is advisable. With any treatment, however, the prognosis is invariably poor.

## BIBLIOGRAPHY

1. BRESCIA, M. A.: Chylothorax; report of case in infant, *Arch. Pediat.*, 1941, lviii, 345.
2. QUINCKE: *Deutsch. Arch. f. Klin. Med.*, 1875, xvi, 121.
3. VAN NUYS, R. G.: Chylothorax; report of case, *California and West. Med.*, 1931, xxxiv, 269.
4. NOWAK, S. J. G., and BARTON, P. N.: Chylothorax; report of a case arrested by phrenicotomy, *Jr. Thoracic Surg.*, 1941, x, 628.
5. HØYER, A.: Chylothorax, *Nord. Med. (Norsk Mag. f. Laegevidensk.)*, 1941, ix, 40.
6. HARRELL, G. T., STREET, D. M., and REISER, R.: Chylothorax and chylous ascites; report of case with lipid analyses, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 1045.
7. EVERHART, J. K., and JACOBS, A. H.: Chylothorax—review of literature and report of case in newborn infant, *Jr. Pediat.*, 1939, xv, 558.
8. GORDON, J.: Traumatic chylothorax; case report, *Ann. Int. Med.*, 1940, xiii, 1998.
9. COOKSON, H. A., and SLADE, D. A.: True chylous pleurisy, *Lancet*, 1940, ii, 477.
10. CELLAN-JONES, C. J., and MURPHY, W.: Traumatic chylothorax, *Brit. Med. Jr.*, 1940, ii, 590.
11. MATSON, R. C., and STACY, J. W.: Traumatic chylothorax; case, *Dis. of Chest*, 1940, vi, 332.
12. SULLIVAN, J. T.: Traumatic rupture of the left lobe of the liver and rupture of the left diaphragm with left chylothorax, *Am. Jr. Surg.*, 1941, li, 423.
13. SMITH, D. D., and WOLIVER, E.: Traumatic chylothorax, *Arch. Surg.*, 1941, xliii, 627.
14. DORSEY, J. F., and MORRIS, G. E.: Traumatic rupture of the thoracic duct with chylothorax, *Jr. Am. Med. Assoc.*, 1942, cxix, 337.
15. DOUADY, D., DUPUY, D., and BOUVRAIN, V.: Benign chylothorax after section of pleural adhesions in pulmonary tuberculosis; case, *Arch. med.-chir. de l'app. respir.*, 1938, xiii, 284.
16. FUJITA, K., BANDO, T., and SUGISHITA, J.: Traumatic chylothorax, *Arch. f. jap. Chir.*, 1939, xvi, 229.
17. CERCAS, E.: Latescent hydrothorax; clinical study of case of chyloform hydrops, *Rev. clin. espan.*, 1940, i, 437.
18. CZIGLÁNY, F.: Chylothorax; case in infant, *Kinderärztl. Praxis*, 1941, xii, 140.
19. LAMARTINE DE ASSIS, J., and RAINO, L.: Chyloform pleural and peritoneal effusion due to primary lymphosarcoma of retroperitoneal lymph nodes; case, *São Paulo med.*, 1941, i, 41.
20. FOFFANI, G.: Recurrent traumatic bilateral chylothorax; case, *Gazz. d. osp.*, 1941, lxii, 395.

21. HEPPNER, G. J.: Bilateral chylothorax and chyloperitoneum, *Jr. Am. Med. Assoc.*, 1934, cii, 1294.
22. McNABB, D. S., and SCARLETT, E. P.: Traumatic chylothorax due to intrathoracic rupture of the thoracic duct, *Canad. Med. Assoc. Jr.*, 1932, xxvii, 29.
23. SHACKELFORD, R. T., and FISHER, A. M.: Traumatic chylothorax, *South. Med. Jr.*, 1938, xxxi, 766.
24. FINKELSTEIN, B. K.: Tears and injuries of the thoracic duct, *Bolnichn. Gaz. Botkina*, 1901, xxii, 914.
25. BEATTY, O. A.: Chylothorax; case report, *Jr. Thoracic Surg.*, 1936, vi, 221.
26. STRAUS, A.: Chylothorax due to bullet wound of thoracic duct and syndrome of traumatic chylothorax; report of case and seven cases from literature, *Jr. Thoracic Surg.*, v, 539.
27. GAUDIN, S.: Pathogenese und Klassifikation der milchartigen Ergüsse, *Ergebn. d. inn. Med. u. Kinderh.*, 1913, xii, 218.
28. WALLIS, R. L., and SCHÖLBERG, H. A.: On chylous and pseudochylous ascites, *Quart. Jr. Med.*, 1910, iii, 301.
29. LILLIE, O. K., and FOX, G. W.: Traumatic intrathoracic rupture of the thoracic duct with chylothorax, *Ann. Surg.*, 1935, ci, 1367.
30. MOUCHET, A.: Le chylothorax traumatique, *Jr. de chir.*, 1933, xlii, 386.
31. OEKEN: Ein Fall von Zerreißung des Ductus thoracicus infolge Brustquetschung, *München. med. Wchnschr.*, 1908, lv, 1182.
32. BAUERSFELD, E. H.: Traumatic chylothorax from ruptured thoracic duct treated by intravenous injection of aspirated chyle, *Jr. Am. Med. Assoc.*, 1937, cix, 16.
33. BROWN, A. L.: Traumatic rupture of thoracic duct with bilateral chylothorax and chylous ascites: new operation; report of a case, *Arch. Surg.*, 1927, xxxiv, 120.

## CHORDOMATA: A REVIEW OF THE LITERATURE, WITH REPORT OF A SACROCOCCYGEAL CASE \*

By DANIEL B. FAUST, M.D., F.A.C.P., HUGH R. GILMORE, JR., M.D., F.A.C.P.,  
and CHARLES S. MUDGETT, M.D., F.A.C.P., *New Orleans, Louisiana*

### INTRODUCTION

CHORDOMATA are tumors that arise from remnants of the fetal notochord. These remnants may be situated in any of the intervertebral discs and in the region of the spheno-occipital or sacro-coccygeal articulations. They rarely occur in the mandible or maxilla. These notochordal remnants frequently give rise to small tumors termed ecchordosis physaliphora by Luschka<sup>1</sup> in 1856, and by Virchow<sup>2</sup> in 1857. Virchow considered these tumors to be of cartilaginous origin, but Ribbert,<sup>3</sup> supported by Müller's<sup>4</sup> theory, believed that they arose from remnants of notochordal tissue. Ribbert noted the resemblance of the cells to those of the notochord, and furthermore produced experimental evidence to support his view. Remnants of notochordal tissue persist in the nucleus pulposus of the intervertebral discs of vertebrates. Ribbert punctured the intervertebral disc of a rabbit allowing the nucleus pulposus to extrude. A tumor resembling chordoma developed at the site of the injury.

\* Received for publication July 13, 1942.

From the Medical and Laboratory Services, Walter Reed General Hospital, Washington, D. C.

## EMBRYOLOGY

The notochord develops from the entoderm, and in the embryo lies as a solid cord extending lengthwise of the body, ventral to the neural canal. As the embryo develops, mesodermal tissue surrounds the notochord and from this mesodermal tissue the vertebrae and intervertebral discs develop. The notochord thus is embedded in the bodies of the vertebrae and in the intervertebral discs. The vertebral portion disappears, but in the discs notochordal tissue persists as the nucleus pulposus. In its earliest stages, the notochord is first a hollow tube, and then a solid cord of non-vacuolated, polygonal, undifferentiated epithelial cells surrounded by a hyaline-like sheath. Later, the cells become vacuolated. These vacuoles contain a gelatinous, mucin-like substance which later escapes from the cell, forming a mucinous matrix in which lie syncytial-like groups of cells.

Bruce and Mekie<sup>5</sup> consider that chordomata resembling the early stages of the developing notochord are most malignant and those resembling the later stages, least malignant. Bérard, Dunet, and Peyron,<sup>6</sup> and Linck and Warstadt,<sup>7</sup> in a study of human embryos, demonstrated notochordal tissue lying on the surface of the vertebral bodies chiefly in the lumbosacral area. These portions of the notochordal tissue on the surface of the vertebral column were connected with the notochord itself by thin strands of notochordal tissue. Chordomata probably arise from these misplaced notochordal tissues. Another possibility is that they arise from the nucleus pulposus with injury as a contributing factor, in a few instances. A history of antecedent trauma was noted in 14 cases by Peyron and Melissinos<sup>8</sup> in 1935. In the cranial region, nodules of notochordal tissue are found lying on the Clivus Blumenbachii in about 2 per cent of autopsies. Tumors may develop from these nodules, and project into the cranial cavity, in the sphenoidal sinus, or into the pharynx.

Bruce and Mekie<sup>5</sup> stated "that once encased in bone, the notochordal tissue does not usually survive, but in the absence of a bony envelope it may, and often does, persist. In the situations where normal persistences have been shown to be likely, there is the further feature that the notochordal tissue is not even restrained by a sheath of fibrous tissue as in the case of the nucleus pulposus of the discs."

## HISTOLOGY

In 1922, Alexais and Peyron<sup>9</sup> presented a comprehensive study on the histogenesis and origin of chordomata. Their report was based upon the examination of nine tumors. They stated that vacuolization of the cellular elements affecting the cytoplasm and intercellular spaces about the ectoplasm was a specific characteristic of chordal tissue. They also stated that the vacuoles contained a substance of a mucin-like character. The cells may be arranged in groups, about cavities, and appear prismatic or cuboidal in shape. There may be plain cellular strips of epithelial type with dense cytoplasm filled with vacuoles, interspaced regularly with vascular endothelium. There may be cellular elements of a fusiform or polymorphous type, analogous to those of sarcomata. Lastly, there may be a network of fibrils of a remarkable fineness, appearing in the vacuolized zones, coincident with a syncytial evolution which makes the cellular limits disappear almost completely.

The stage of non-vacuolated polygonal cells is said to be the most malignant type of chordoma. The stage of vacuolated mucin-containing cells is of moderate malignancy. The syncytial stage of intercellular mucoid degeneration is said to be the most benign type of chordoma. Fletcher, Woltman, and Adson,<sup>10</sup> in 1935, summarized the histopathologic characteristics of chordomata as follows: "(1) the formation of intracellular and extracellular mucus; (2) the presence of physaliphorous or huge vacuolated mucus-containing cells; (3) the lobular arrangement of the tumor cells, which usually grow in cords; (4) the occasional occurrence of vacuolation of the nuclei; and (5) the close resemblance to notochordal tissue as seen in the nuclei pulposi of the intervertebral discs."

### HISTORICAL

In 1925, Coenen<sup>11</sup> gave the following classification of chordomata: (1) cranial, including the clivus chordoma (both benign and malignant), the hypophyseal, and the nasopharyngeal chordomata; (2) vertebral chordomata; and, (3) caudal or sacrococcygeal chordomata, including the antesacral, retrosacral, and central forms. This classification is still used.

Remnants of notochordal tissue were first found by Klebs,<sup>12</sup> in 1864, in the sphenoccipital region. In 1903, Grahl<sup>13</sup> reported the first case of sphenoccipital chordoma. Trélat,<sup>14</sup> in 1868, reported a case of chondroma of the neck, which at operation was found attached to the cervical vertebrae. This case was thought by DesJardines<sup>15</sup> and again by Owen, Hershey, and Gurdjian,<sup>16</sup> in 1932, to have been a chordoma. The case reported by Raul and Diss,<sup>17</sup> in 1924, was the first authentic case of vertebral chordoma in which the tumor was located in the cervical region. In 1900, Hennig<sup>18</sup> reported the first case of sacrococcygeal chordoma. Since then many cases in both the sphenoccipital and sacrococcygeal regions, and a few vertebral cases have also been reported.

### RÉSUMÉ OF CASES

There have been several comprehensive reviews of the reported cases in the past. The first of these was in 1922 by Stewart,<sup>19</sup> followed by Eckel and Jacobs<sup>20</sup> in 1925, and Coenen<sup>11</sup> again in 1925. In 1926, Stewart and Morin<sup>21</sup> reported a total of 55 cases distributed as follows: (1) region of sphenoccipital synchondrosis—25, (*a*) projecting into the cranium—16; (*b*) projecting into the nasopharynx only—1; (*c*) projecting in both directions—8; (2) occipital region—1; (3) upper and lower jaw—1; (4) sacrococcygeal region—27, (*a*) projecting anteriorly—12; (*b*) projecting posteriorly—8; (*c*) projecting in both directions—7. They found that approximately 70 per cent occurred in males, and that the average age incidence was 34.9 years for the sphenoccipital chordomata, and 50.6 years for the sacrococcygeal region, with a variation from 16 to 72 years. The limits of duration in the cases they studied were from two to eight years. Since then, cases have been reported in infants and very young children by Montgomery and Wolman<sup>22</sup> in 1933.

In 1930, Machulko-Horbatzewitsch, and Rochlin<sup>23</sup> reviewed a series of 103 reported cases, and found 49 cranial cases, eight vertebral cases, and 46 caudal cases. In 1935, Mabrey<sup>24</sup> reviewed 150 cases, and found 49 were in the cranial region, seven in the cervical, two thoracic, five lumbar, and 87 sacrococcygeal.

### TABLE I

Year	Author	No. of Cases
1927	Ajello <sup>25</sup>	1
1931	Klotz <sup>26</sup>	1
1933	Kling <sup>27</sup>	1
1934	Traina <sup>28</sup>	1
1934	Haas <sup>29</sup>	1
1934	Camauer and Sacon <sup>30</sup>	1
1934	Harbitz <sup>31</sup>	1
1935	Livingston <sup>32</sup>	1
1935	Furflow <sup>33</sup>	1
1935	Adson et al. <sup>34</sup>	2
1935	Van Wagenen <sup>35</sup>	2
1935	Fidlovosky <sup>36</sup>	1
1936	Cusenza <sup>37</sup>	1
1936	Stevenson and Freidman <sup>38</sup>	2
1936	Gould <sup>39</sup>	1
1936	Boemke and Joest <sup>40</sup>	2
1936	Gutierrez and Monserrat <sup>41</sup>	1
1937	Argaud et al. <sup>42</sup>	1
1937	Braitenberg <sup>43</sup>	3
1937	Dickson et al. <sup>44</sup>	1
1937	Hryniewicz <sup>45</sup>	1

Year	Author	No. of Cases
1937	Roche and Martin <sup>46</sup>	1
1937	Szeker <sup>47</sup>	1
1938	Peers <sup>48</sup>	1
1938	Ridpath <sup>49</sup>	2
1938	Schneegans and Mandigas <sup>50</sup>	1
1938	Calamandrai <sup>51</sup>	1
1938	Remaggi <sup>52</sup>	1
1939	Zambrini and Castellanos <sup>53</sup>	1
1939	Moller <sup>54</sup>	1
1941	Zeitlin and Levinson <sup>55</sup>	1
1941	Boldrey and McNally <sup>56</sup>	4
1941	Gardner and Turner <sup>57</sup>	3
Total since 1935		45
Total reported by Mabrey . . . . .		47
		TOTAL 92

Year	Author	No. of Cases	Year	Author	No. of Cases
1926	Karsner (from Stewart) <sup>19</sup>	1	1937	Bruce and Mekie <sup>5</sup>	2
1933	Grandclaude et al. <sup>58</sup>	1	1937	Braitenberg <sup>43</sup>	2
1935	Pupo and Tarafa <sup>59</sup>	1	1938	Ghareeb <sup>72</sup>	2
1935	Fletcher et al. <sup>60</sup>	7	1938	Ruckensteimer <sup>73</sup>	1
1935	Roche et al. <sup>61</sup>	1	1938	Bobbio <sup>74</sup>	1
1936	Schwartz et al. <sup>62</sup>	1	1938	Nagase <sup>75</sup>	1
1936	Harmos and Palmer <sup>63</sup>	1	1939	Ashour <sup>76</sup>	1
1936	Hsieh and Hsieh <sup>64</sup>	1	1939	Lyall <sup>77</sup>	1
1936	Gabriel <sup>65</sup>	1	1940	Mixter and Mixter <sup>78</sup>	1
			1940	Bowers <sup>79</sup>	1
1936	Simonds <sup>66</sup>	2	Total since 1935 Total reported by Mabrey		35
1937	Cazzamali <sup>67</sup>	1			87
1937	Schwyzzer <sup>68</sup>	1	TOTAL 122		—
1937	Nash and Laskey <sup>69</sup>	1			
1937	Barnes and Owen <sup>70</sup>	1			
1937	Coley <sup>71</sup>	1			



TABLE III  
Vertebral and Other Chordomata Reported since 1935

Year	Author	No. of Cases	Year	Author	No. of Cases
1868	Trélat <sup>14</sup>	1	1938	Bertoni and Fratini <sup>92</sup>	1
1887	Hermann and Tourneaux <sup>80</sup>	1	1939	Güthert <sup>93</sup>	1
			1940	Mixter and Mixter <sup>78</sup>	2
			1940	Richards and King <sup>94</sup>	1
1889	Klebs <sup>81</sup>	1	Total since 1935		20
1926	Andler <sup>82</sup>	1	Total reported by Mabrey		14
1928	Dowling and Sepich <sup>83</sup>	1	TOTAL 34		—
1929	Hutton and Young <sup>84</sup>	1			
1929	Hermann <sup>85</sup>	1		Others	
1930	Rocher and Guerin <sup>86</sup>	1	1934	Landivar (jaw) <sup>95</sup>	1
1934	Harbitz <sup>87</sup>	1	1939	Ashour <sup>76</sup>	1
1935	Fletcher et al. <sup>10</sup>	1		(ant. larynx)	
1935	Ellis <sup>88</sup>	1			
1935	Adson et al. <sup>34</sup>	1	Total since 1935		2
1936	Ohein <sup>89</sup>	1	Total reported by Mabrey		2
1936	Albert <sup>90</sup>	1	TOTAL 4		—
1937	Cabot <sup>91</sup>	1			

We have reviewed the literature and those cases not included in Mabrey's list, and those that have been reported since 1935 are included (tables 1, 2, and 3). The number of cases found in each location is as follows: (1) cranial (including spheno-occipital and nasopharyngeal cases)—92; (2) vertebral—34; (3) caudal (or sacrococcygeal)—122; (4) others—4. Thus it will be seen that 48.4 per cent of the reported cases are found in the sacrococcygeal region, and 36.5 per cent in the cranial region, the remainder being located along the vertebral column, with few exceptions.

#### SYMPTOMATOLOGY

The signs and symptoms of the cranial chordomata are those of a brain tumor, or a tumor of the nasopharyngeal cavity, with headache and diplopia, or difficult nasal breathing among the most common symptoms, as the case may be. Nausea, vomiting, and vertigo are also frequently found. Involvement of one or several of the cranial nerves from the pressure of the growth almost always occurs, with consequent pupillary changes, disturbances of the senses of smell, vision, and occasionally hearing and speech. There may be strabismus, hemianopsia, optic atrophy, papilledema, nystagmus, dilatation of the pupil, and loss of light and consensual reflexes, depending upon the cranial nerves involved in the new growth. The involvement is most frequently unilateral, but occasional bilateral involvement has been noted. Hemiplegia, paraplegia, incontinence of urine and feces, and peripheral muscle weaknesses have been reported. Loss of weight and general weakness occur infrequently. In those cases in which the growth is predominantly anterior, difficult breathing results from the protrusion of the growth into the nasopharynx, and occasionally the posterior segment of

the nose. Epistaxis occasionally occurs in such cases. The mass may be seen or palpated in the nasopharynx when the latter is involved. Roentgenograms may or may not show signs of increased intracranial pressure, with erosion or destruction of the bones in the region of the spheno-occipital articulation or the sella turcica.

The signs and symptoms of chordomata of the spine are those of pressure, due to the increasing size of the tumor mass. The growth may progress anteriorly or posteriorly, as in other regions, or remain centrally located. It frequently causes erosion of the adjacent vertebrae. In the upper cervical region the growth may protrude into the pharynx, with consequent difficulty in swallowing or respiration. In the lower cervical region, the progress of growth may be into the lateral or posterior neck muscles, the mass being visible externally, and causing painful and difficult neck movements. Coincident with these symptoms, those due to pressure on the brachial plexus and the spinal cord arise, with various paralyses and paresthesias or anesthetic areas, either in one or both of the upper extremities. When the tumor mass encroaches on the cord, whether in the cervical, dorsal, or lumbar region, the signs are those of a spinal cord tumor, with sphincter paralyses, either unilateral or bilateral paralyses of the muscles below the level of the tumor, and the development of areas of hypoaesthesia, or anesthesia. The deep reflexes of the involved areas may be either increased or decreased. Ankle clonus may develop.

In the dorsal region, the growth is most commonly into the mediastinum, with pressure on the aorta or the esophagus, resulting in pain in the chest, frequently substernal, and difficulty in swallowing. There may be more or less complete obstruction of the esophagus. In the lumbar region, pressure on abdominal organs may cause symptoms referable to these organs, in addition to those symptoms noted above.

As in cranial and vertebral chordomata, the signs and symptoms of sacrococcygeal chordomata are those due to the pressure of the gradually increasing tumor mass and its encroachment on structures in the pelvis. The tumor most frequently grows anteriorly and is palpable as a firm mass in the rectal pouch on digital examination, or seen on proctoscopic examination to be obstructing the rectum or constricting its lumen, and digital examination may show the mass more or less completely filling the pelvic cavity if it is in an advanced stage. In large growths in this region, the ureters may be displaced and the bladder pressed upon. Consequently, there may be difficulty in defecation and occasionally in micturition. The feces may be blood stained, or there may be frank hemorrhage from the rectum. The tumor may extend posteriorly, and if so, appears as a mass of variable size, occasionally of tremendous size, over the sacrum or nates. Growth may progress both posteriorly and anteriorly, or into the abdomen, as in the case we are reporting. Paralyses, hypoaesthesias, or anesthetic areas of one or both the lower extremities develop as a result of the pressure of the tumor mass. Pain over the mass, in the rectum, and radiating over the course of the involved nerves is frequent. Difficulty in walking may be an early symptom.

The roentgenographic signs of sacrococcygeal chordomata were stated in 1936 by Hsieh and Hsieh<sup>64</sup> as: "1. *Expansion*. This may be demonstrated in the antero-posterior or lateral views, preferably by stereoscopic examination of

the bone which may or may not be entirely preserved. 2. *Rarefaction or Destruction*. The involved bone presents either a loculated appearance with multiple small circular or oval radiotranslucent areas or the bone is destroyed in large areas. 3. *Trabeculation*. The remains of the undestroyed bone form dense trabeculae which may extend into the soft tissue mass outside the original normal boundary of the bone. 4. *Calcification*. This may be due to reactive new bone formation or deposit of calcified material in the tumor as a result of degeneration or necrosis. This calcified matter appears usually in irregular masses of soft radio-opacity." They stated that these "findings elsewhere in the skeleton may indicate giant-cell tumor, osteochondroma, or myxochondroma, but the clinical picture and particularly the sacrococcygeal location of the lesion should suggest the diagnosis of chordoma."

Similar roentgenographic findings may be noted when the tumor is located in the vertebral column or in the cranium, if the tumor has been one of comparatively long standing, but these findings are not at all of a positive diagnostic nature. Roentgenograms are frequently entirely normal even in well advanced cases.

Encephalograms and myelograms may be of distinct aid in localizing or discovering the presence of a cranial or spinal chordoma, but the proof that the lesion is a chordoma must wait an examination of the tissue microscopically.

#### DIFFERENTIAL DIAGNOSIS

The nature of the tumor when found cannot be definitely stated without microscopic examination of the tissue, but it can be continually borne in mind in considering the types of tumors that are located in the spheno-occipital or the sacrococcygeal region, and should not be forgotten in tumors of the vertebral column. A histopathological diagnosis is at times most difficult as there may be elements in the tissue which would strongly resemble those found in myxochondroma or sarcoma, or gelatinous carcinoma of the rectum. If the tumor mass surrounds the rectum a gelatinous carcinoma of the rectum may be strongly considered, but a chordoma is more firmly attached to the sacrum by strands of attachment than is a carcinoma. The histologic features of chordomata have been discussed in detail above. Teratomata, dermoid cysts, enchondromata, osseous sarcomata, myelomata, tuberculosis of the sacrum, and carcinomata of the rectum must all be differentiated from sacrococcygeal chordomata. Diagnostic puncture of the tumor mass, when accessible, is of aid in establishing a diagnosis.

Ridpath<sup>49</sup> stated in 1938 that there are "many good reasons for confusing chordoma with craniopharyngioma (a tumor of Rathke's cleft and hypophyseal stalk). The manifestations referable to the cranial nerves, especially defects in the visual fields, and the roentgenographic changes may be identical. There may even be suprasellar calcification, such as is common in a craniopharyngioma. The adenomata and carcinomata of the hypophysis may destroy a considerable amount of bone, and in order to complete the imitation of a chordoma, they may grow into the nasopharynx." In spheno-occipital chordomata "there is little or no evidence of hypophyseal dysfunction." He stated that among the other tumors to be differentiated are parasellar meningiomata, atypical chondro-

mata, chondrosarcomata, myxosarcomata, pharyngeal dermoid cysts, teratomata, and primary nasopharyngeal carcinomata.

### PROGNOSIS

Benign and malignant chordomata are both notably rather slow in growth. In the former, the process may cover a period of many months or several years before the symptoms are pronounced enough for the patient to seek relief. In the latter, the progress of growth is likewise variable, but is usually much more rapidly progressive than in the benign type. However, several years may elapse in malignant cases that show definite metastatic lesions at the time of the first examination. As a rule, the cranial type is the most rapidly fatal. Benign growths if not completely removed at operation continue to grow. Metastases in the malignant type occur in the minority of cases, and are found in the adjacent lymph nodes, heart, lungs, liver, spleen, kidneys, and adrenals. The adjacent tissues are frequently involved by direct extension of the growth.

### TREATMENT

In areas that are accessible to surgical removal of the tumor, operation offers the only hope of a permanent cure. If completely removable, recurrence does not occur in the benign type, and complete recovery ensues. Because of the location, size and extent of the growth, and involvement of adjacent structures, complete removal and consequent cure are not often possible. Relief of untoward pressure symptoms with partial removal, however, is indicated whenever possible, even if this requires repeated operations as symptoms recur. Malignant chordomata are, of course, always fatal, unless successfully and completely removed before metastases occur. Surgical removal is often a most difficult and arduous procedure, and in cases in which extensive areas of bone are involved, an impossible task. Roentgen and radium therapy have both been used following operation, and without operation, but with very questionable results. Some relief of pain may result, but little can be expected as far as retarding or curing the tumor when this method of treatment is employed.

### CASE REPORT

H. J. J., colored male, aged 23 years, was admitted to Walter Reed General Hospital, Washington, D. C., on March 24, 1938. His chief complaints were intermittent dull pain in the right lumbar region, loss of weight and strength, a rather harassing productive cough, dyspnea on exertion, anorexia and constipation. His past and family history were irrelevant except that he had had influenza in 1933, and gonorrhea in 1931. The present illness started in the summer of 1937, with a severe nasopharyngitis and bronchitis. His health had declined from then on, the cough becoming chronic and productive of a yellow-grayish material, occasionally streaked with blood. There was a sense of tightness in the chest. During the first part of 1938, the condition became worse, strength failed, and he developed a tendency to perspire, had dyspnea on exertion, constipation, and intermittent dull pain in the right lumbar region.

Physical examination on admission showed a young colored man, underweight and obviously chronically ill. The temperature was 98.8° F., pulse 112, respirations 32. His normal weight had been 135 pounds, and was 114 pounds on admission. The inguinal

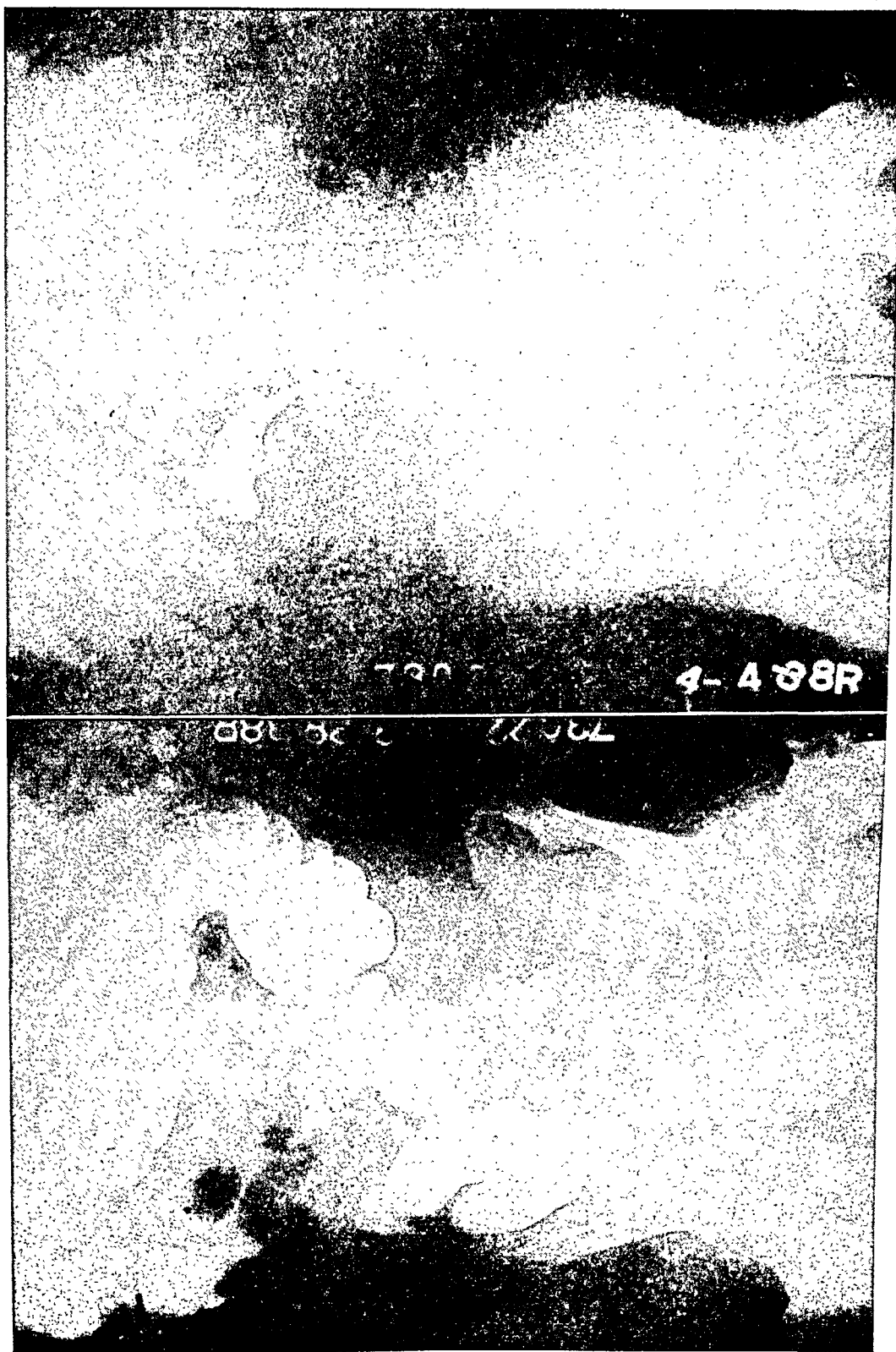


FIG. 1. (Left) Barium enema showing displacement of the descending colon to the left. (U. S. Army, Medical Museum Neg. No. 68292, Acc. No. 62185.)

FIG. 2. (Right) Urogram showing marked displacement of ureter to the left. (U. S. Army Medical Museum Neg. No. 68293, Acc. No. 62185.)

glands were enlarged and firm, and there was a generalized enlargement of all the lymph glands. The tonsils were moderately enlarged. The blood pressure was 124 mm. Hg systolic and 64 mm. diastolic. The heart rate was accelerated, but the heart was otherwise normal. Examination of the lungs showed impaired resonance bilaterally, ranging from dullness to flatness at the posterior right base. There were moist, crackling râles, in the left lower lobe posteriorly and in the axilla. There were diminished breath sounds with prolongation of expiration in the lower right lung. Tactile fremitus was absent in the right base posteriorly. The prostate was soft and somewhat tender. The abdomen was flat, with the liver edge barely palpable. There was a firm fixed mass in the right lower quadrant, extending into the right flank, tender to pressure, appearing attached to the pelvis. The pupils were normal, as were the pupillary reflexes. The knee jerk on the right was absent. Other reflexes were normal.

The blood count on admission was 4,160,000 red cells, hemoglobin 70 per cent, 12,000 white cells, with 72 per cent neutrophils, 19 per cent lymphocytes, 7 per cent monocytes, and 2 per cent eosinophiles. The Wassermann test showed a two plus reaction on two occasions, with the Kahn test four plus on one occasion, and two plus on the second. The blood chemistry was within normal limits. Urinalyses were negative, including cultures. The sputum was negative for tubercle bacilli on repeated examinations. The feces were negative for parasites and ova, free and occult blood. The fractional gastric analysis showed a low total acid curve, with absence of free hydrochloric acid in all but one specimen. A barium enema showed the colon and cecum displaced to the left (figure 1). A flat film of the kidney, ureter and bladder regions showed a faint outline of the mass in the right side of the pelvis. A urogram gave the impression of a tumor mass in the abdomen, in the right lower quadrant, in relation to the right kidney (figure 2). Gastrointestinal studies were negative. Metastatic growths were noted throughout both lungs on roentgenograms taken on admission (figure 3), and these increased in size throughout the period of hospitalization. No metastases were evident in roentgenograms of the lumbar vertebrae, bones of the pelvis, femora, or the skull.

Soon after admission a lymph gland from the right inguinal region was removed and showed on microscopic examination a low grade, chronic, non-suppurative inflammatory reaction. As it was not feasible to make any further attempts at a positive diagnosis, because of the far-advanced nature of the tumor, a working diagnosis of an unknown variety of malignant tumor of the right lower abdomen was made. The possibility of the origin of the tumor at the lower pole of the right kidney was considered. On April 3, 1938, he had a rather severe pain in the right lower extremity, and this recurred at varying intervals and with varying intensity throughout his period of hospitalization. Deep roentgen therapy was started on April 7, 1938, and completed on May 6, 1938. A total of 4,100 r. to six chest fields, and 4,100 r. to three abdominal fields was given, with only slight diminution in the size of the abdominal mass. In June 1938, codeine was required to control the troublesome nocturnal cough, and for the pain in the right lower extremity. In December 1938, deep roentgen therapy was again given, starting on December 1, 1938, and completing the course on January 19, 1939. A total of 1,784 r. was given to the abdominal fields.

During the course of treatment in the hospital a rather severe secondary anemia developed with the red cell count dropping to 2,300,000 and hemoglobin to 50 per cent. The white cell count varied from 3,450 to 18,400, but it was usually within normal limits. Eosinophiles were present on repeated blood counts, and at times were as high as 20 per cent.

The patient remained up and about until the middle of January 1939, when he became much worse, with more pain in the right hip joint, radiating down the right lower extremity, and with considerable aggravation of the productive cough. The

mass in the right lower abdomen had become larger. Morphine was required occasionally to control the pain. By the middle of February 1939, morphine was required four to five times in 24 hours for relief of pain, and cough. The right lower extremity had become mildly edematous. By the middle of March there was moderate edema of both legs and ankles, but he was still able to get out of bed for short periods.

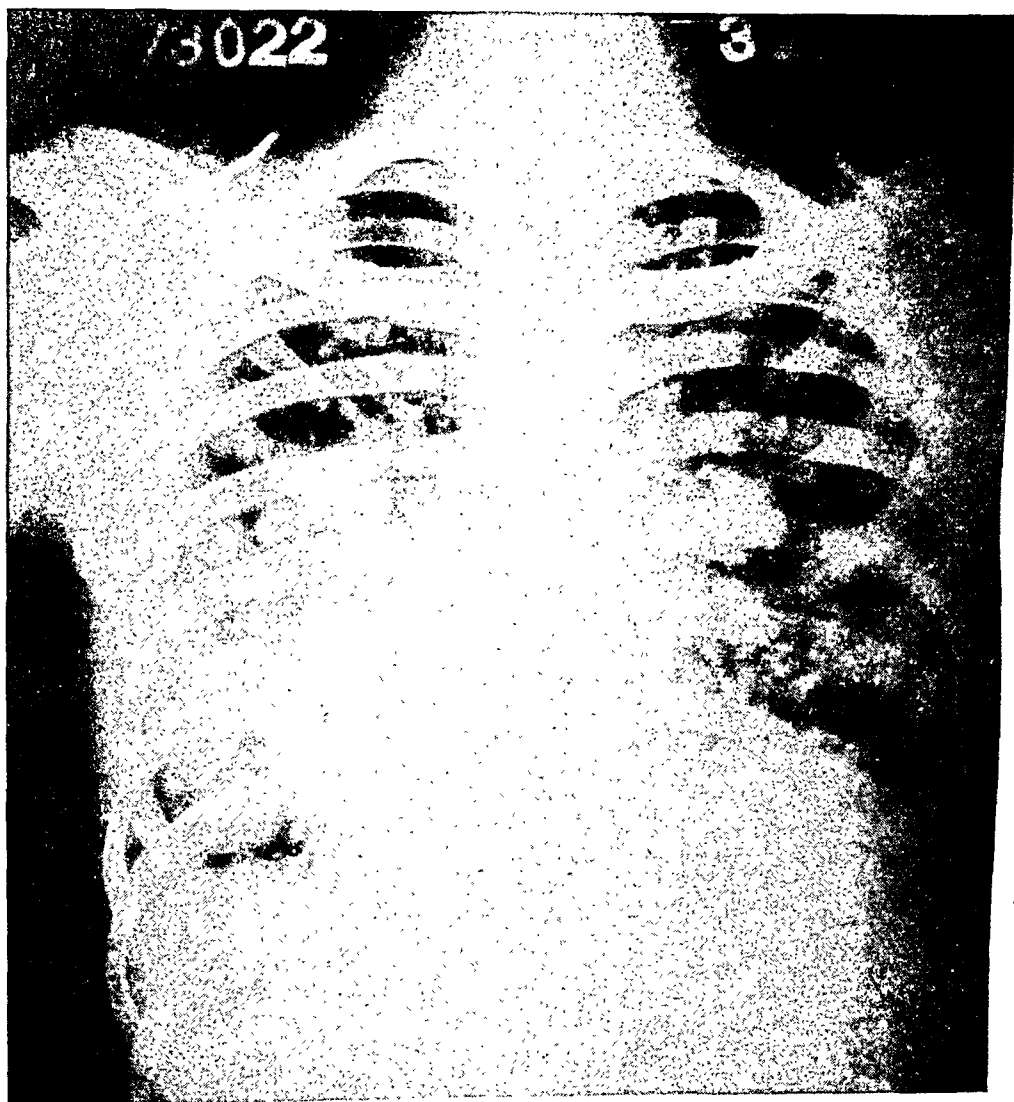


FIG. 3. Roentgenogram of the chest on admission showing metastatic growths throughout both lungs. (U. S. Army Medical Museum Neg. No. 68294, Acc. No. 62185.)

He died quietly on March 21, 1939, at 8:15 a.m. The antemortem diagnosis was retroperitoneal tumor of unknown type, with metastases to the lungs.

*Autopsy.* Gross findings: The skin showed scattered, superficial ulcers, 1 cm. to 2.5 cm. in diameter in the following areas: right mastoid, left ear, face, thorax, abdomen, and back. The right leg and ankle showed moderate edema and the left leg and ankle slight edema.

In the right lower quadrant of the abdomen was a firm, smooth, immovable globular mass which was easily visible projecting above the surface of the abdomen. It measured 15 by 8 cm. The skin was not adherent to the mass.

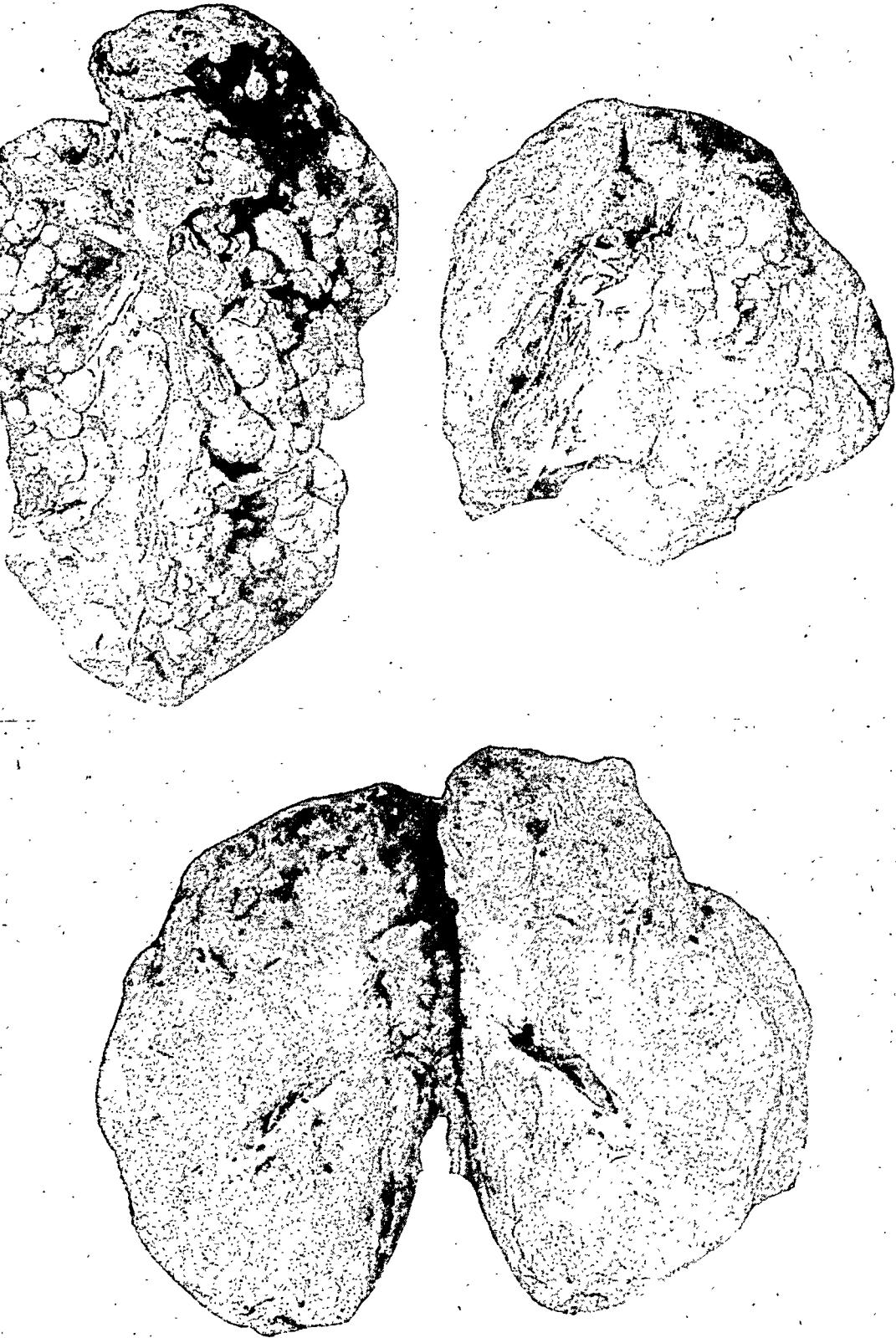


FIG. 4. (Right) Anterior and posterior views of tumor mass removed from right lower abdomen. (U. S. Army Medical Museum Neg. No. 68287, Acc. No. 62185.)  
FIG. 5. (Left) Gross section of tumor showing lobulated surface with areas separated by fibrous septa. (U. S. Army Medical Museum Neg. No. 68289, Acc. No. 62185.)



The right pleural chink contained 500 c.c. and the left pleural chink 100 c.c. of clear, straw-colored fluid. The lungs were free, the right weighing 1,320 grams, and the left 1,020 grams. Both the pleural and cut surfaces of the lung were studded with grayish-white, fairly firm tumor nodules varying in their greatest diameter from

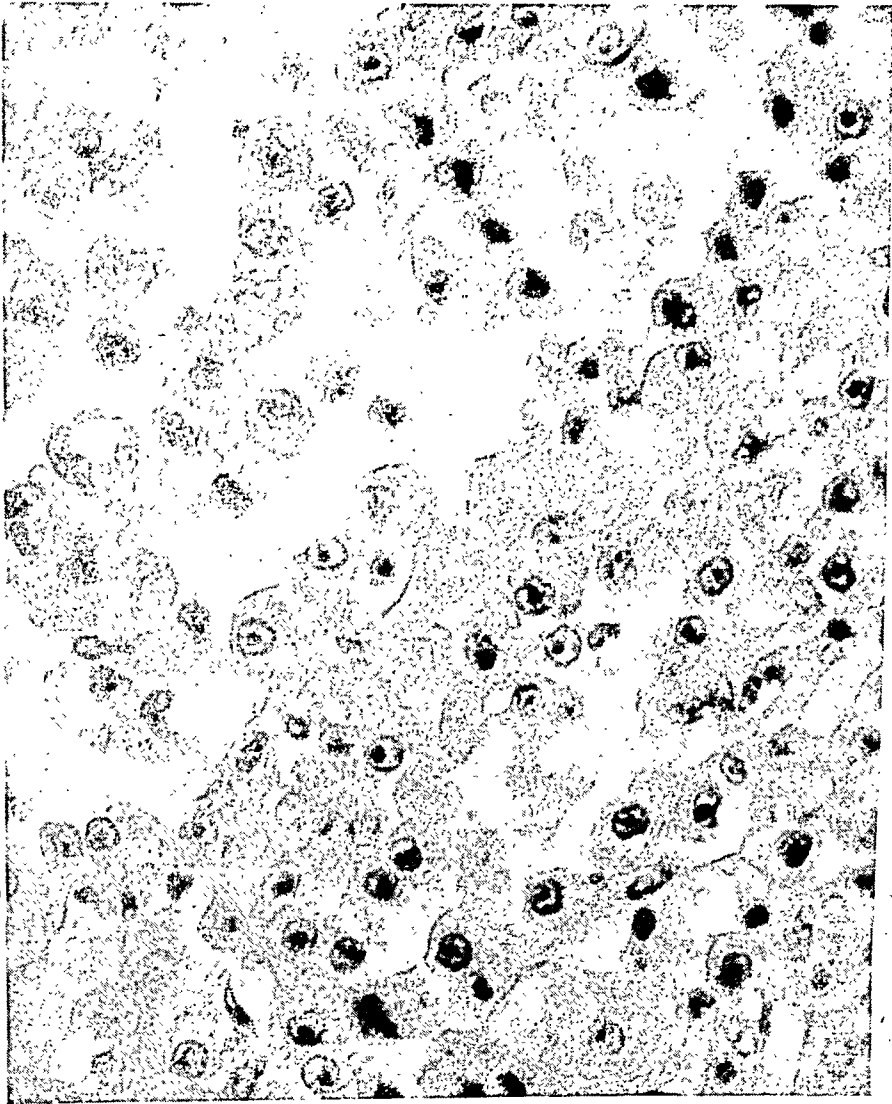


FIG. 6. Large cells with prominent nuclei with occasional vacuoles. (U. S. Army Medical Museum Neg. No. 68666, Acc. No. 60677  $\times$  575.)

0.5 cm. to 4 cm. These nodules were well circumscribed and were distributed throughout all lobes of both lungs. They did not encroach upon bronchi and did not involve the parietal pleura. Mediastinal nodes showed no evidence of tumor.

The cardiovascular system showed no abnormalities.

The peritoneal chink contained about 500 c.c. of clear straw-colored fluid.

The gastrointestinal tract and the mesenteric and retroperitoneal nodes were normal.



FIG. 7. Collection of chordoma cells within the lumen of a small capillary. (U. S. Army Medical Museum Neg. No. 68668, Acc. No. 60677  $\times 575$ .)

No gross lesions were found in the liver, spleen, pancreas, kidneys, bladder, prostate, thyroid or thymus. Sectioning of the left adrenal showed a grayish-white nodule 6 mm. in diameter resembling the nodules seen in the lung:

The tumor measured 20 by 12 by 6 cm. and lay in the right pelvis, extending up over the pelvic brim. It was entirely retroperitoneal with the right ureter running over its surface. The surface was smooth and regular, and the consistency was



FIG. 8. Spaces in mucinous stroma lined by chordoma cells. (U. S. Army Medical Museum Neg. No. 68707, Acc. No. 60677  $\times 240$ .)

firm (figure 4). It was not adherent to any portion of the gastrointestinal tract. The tumor was easily freed laterally but was firmly adherent to the right psoas muscle and to the antero-lateral surface of the sacrum. After removal an area of erosion about 4 cm. in diameter was palpated at the point of attachment to the sacrum. The inferior venà cava and right iliac veins were dilated where they were pushed forward by the tumor.

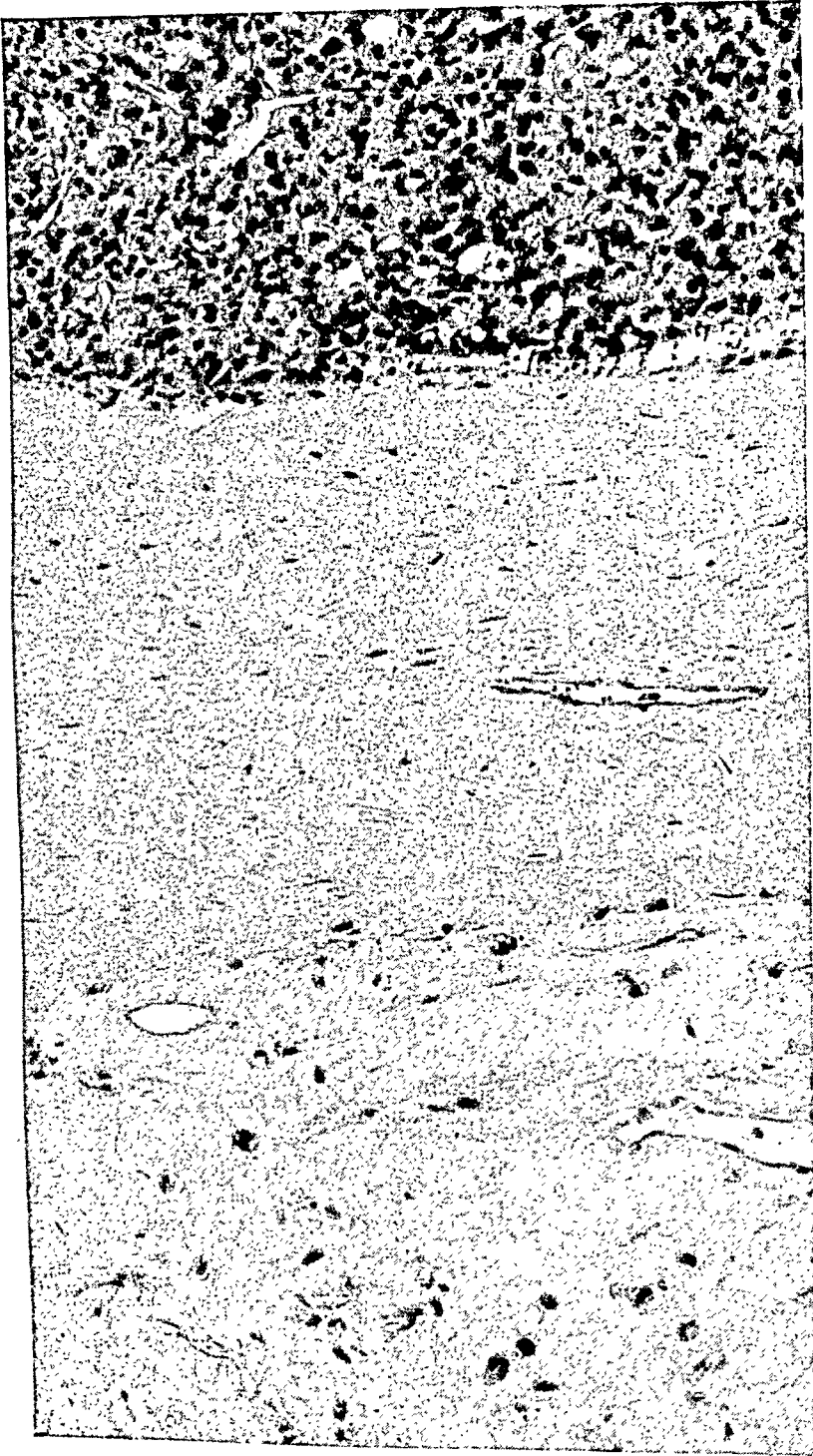


FIG. 9. Area showing almost acellular fibrillar material with scattered vacuolated chordoma cells giving the appearance of cartilage. (U. S. Army Medical Museum Neg. No. 68677, Acc. No. 60677  $\times 17$ .)

Sectioning of the tumor showed a coarsely lobulated surface with moderately soft, grayish-white areas separated by thick fibrous septa. In some areas these septa had a shiny, mucinous or cartilaginous appearance. Small cyst-like areas of degeneration were present and some areas showed a reddish-yellow color suggesting hemorrhage and degeneration (figure 5).

The skull was not opened.

**Microscopic findings:** The histologic picture varied. In some areas the cells were in compact masses with encircling, indistinct strands of supporting tissue which stained black with the Wilder silver stain. The tumor cells themselves were large, with pink staining (hematoxylin and eosin stain) granular cytoplasm and vesicular nuclei with a distinct nucleolus and scattered chromatin granules. Nuclei were rarely hyperchromatic and mitotic figures were not found. Cell borders were often indistinct, frayed or broken, leaving irregular clear areas in the cytoplasm (figure 6). Occasional cells presented distinct cytoplasmic vacuoles. Larger cells showed two to four nuclei. Some of the large cells were more acidophilic than others. Capillaries were rather numerous with occasional larger thin-walled vessels (figure 7). Areas of hemorrhage were present and some areas were necrotic. In other areas, elongated, cyst-like spaces were lined by tumor cells which were frequently in a single layer and stood out distinctly as individual cells supported by a thin strand of connective tissue (figure 8). The lumen contained varying numbers of unsupported cells. These cyst-like spaces lay in a matrix of pink staining, almost acellular fibrillar material. In some areas this pink staining material with scattered vacuolated tumor cells gave the appearance of cartilage (figure 9). With the Van Gieson stain this intercellular substance stained pale pink to a bright red, and a bright blue with the Masson trichrome stain.

A section, including a portion of the right psoas muscle, showed tumor cells among the muscle fibers and in several areas tumor cells were seen in vessels.

In sections of the metastatic lesions in the lungs, the tumor cells were in compact masses with little intercellular substance. Vacuoles were present in some cells, but there was no resemblance to cartilage.

The lesions in the left adrenal presented compact masses of cells, and also the cyst-like spaces seen in the primary tumor. Intercellular material was scant. All metastatic lesions were well circumscribed.

Mayer's mucicarmine stain showed no mucin in sections of the primary tumor or metastatic lesions.

Sections of the prostate and testes showed atrophy and fibrosis, probably secondary to radiotherapy. Microscopic examination of sections of the other organs was normal.

The histologic diagnosis of the tumor and metastatic lesions was chordoma.

## CONCLUSIONS

1. Chordomata are tumors arising from remnants of the fetal notochord, which persist in the intervertebral discs and in the region of the spheno-occipital and sacrococcygeal articulations, and rarely in other regions adjacent to the skull and vertebral column. They may be relatively benign or more frequently malignant, with or without metastases. They may be amenable to surgical removal but usually it is a difficult procedure to remove the tumor mass completely, because of the location. Roentgen and radium therapy are of questionable value. A fatal termination in the course of one to six years is the rule, but cures have been reported following surgical removal.

2. The literature has been reviewed, and a case of a large malignant sacrococcygeal chordoma, extending into the right lower quadrant of the abdomen, with extensive pulmonary metastases and adrenal metastases, has been presented.

3. An outline of the clinical features of cranial, vertebral, and sacrococcygeal chordomata, with the histologic findings, has been presented.

## BIBLIOGRAPHY

1. LUSCHKA, H. VON: Die Altersveränderungen der Zwischenwirbelknorpel, Virchow's Arch. f. path. Anat., Berlin, 1856, ix, 311.
2. VIRCHOW, R.: Untersuchungen über die Entwicklung des Schädelgrundes im gesunden und krankhaften Zustände und über den Einfluss derselben auf Schädelform, Gesichtsbildung und Gehirnbau, 1857.
3. RIBBERT and STEINER, H.: Über die Ecchondrosis physalifora spheno-occipitalis, Centralbl. f. allg. Path. u. path. Anat., 1894, v, 457-461.
4. MÜLLER, H.: Ueber das Vorkommen von Resten der Chorda dorsalis bei Menschen nach der Geburt und über die Verhältnisse zu den Gallerigeschwülsten am Clivus, Ztschr. f. rationelle Med., 1858, ii, 202.
5. BRUCE, J., and MEKIE, R.: Chordoma, Surg., Gynec., and Obst., 1937, lv, 40-47.
6. BÉRARD, L., DUNET, C. L., and PEYRON, A.: Bull. d. Assoc. franç. p. l'étude du cancer, 1922, xl, 28.
7. LINCK and WARSTADT: Origin and localization of malignant chordomas, especially in sacrococcygeal region, Beitr. z. klin. Chir., 1922, cxxxvii, 612-626.
8. PEYRON, A., and MELISSINOS, J.: Chordome, tumeur traumatique, Ann. de méd. lég., 1935, xv, 478-488.
9. ALEXAIS and PEYRON: Sur l'histiogenese et l'origine des chordomes, Compt.-rend. Acad. d. sc., 1922, clxxiv, 419.
10. FLETCHER, E. M., WOLTMAN, H. W., and ADSON, A. W.: Sacrococcygeal chordomas; clinical and pathologic study, Arch. Neurol. and Psychiat., 1935, xxxiii, 283-299.
11. COENEN, H.: Das Chordom, Beitr. z. klin. Chir., 1925, cxxxiii, 1-77.
12. KLEBS, E.: Ein Fall von Ecchondrosis spheno-occipitalis amylacea, Virchow's Arch. f. path. Anat., 1864, xxxi, 396.
13. GRAHL, O.: Eine Ecchondrosis physalifora spheno-occipitalis (Chordom des Turken-sattels) ungewöhnlichen Umfangs mit interessanten klinischen Folgen, Inaug. Dissert., Göttingen, 1903.
14. TRÉLAT: Encondroma a marche rapide, Gas. d'hôp., 1868, xli, 254.
15. DESJACQUES, R.: A propos d'un case de chondrome de la colonne cervicale, Lyon chir., 1927, xxiv, 40.
16. OWEN, C. I., HERSHEY, L. N., and GURDJIAN, E. S.: Chordoma dorsalis of the cervical spine, Am. Jr. Cancer, 1932, xvi, 830-840.
17. RAUL and DISS: Quoted by MABREY, R. E.<sup>24</sup>
18. HENNIG, L.: Über congenitale echte Sakraltumoren, Beitr. z. path. Anat. u. z. allg. Path., 1900, xxviii, 593-619.
19. STEWART, M. J.: Malignant sacrococcygeal chordoma, Jr. Path. and Bact., 1922, xxv, 40-62.
20. ECKEL, J. L., and JACOBS, W. F.: Malignant spheno-occipital chordoma, report on case, Jr. Nerv. and Ment. Dis., 1925, lxi, 471-486.
21. STEWART, M. J., and MORIN, J. E.: Chordoma, a review with report of a new sacrococcygeal case, Jr. Path. and Bact., 1926, xxix, 41-60.
22. MONTGOMERY, A. H., and WOLMAN, I. J.: Sacrococcygeal chordomas in children, Am. Jr. Dis. Child., 1933, xli, 1263-1281.
23. MACHULKO-HORBATZEWITSCH, G. S., and ROCHLIN, L. L.: Clinical study, pathomorphology and histogenesis of chordomas, Arch. f. Psychiat., 1930, lxxxix, 222-262.

24. MABREY, R. E.: Chordoma, study of 150 cases, *Am. Jr. Cancer*, 1935, xxv, 501-517.
25. AJELLO-AINTO, L.: Contributo casistico allo studio del cordoma del clivus di Blumenbach, *Cultura méd. mod.*, 1927, vi, 39-48.
26. KLOTZ, A.: Malignant chordoma of nasopharynx; case, *Semaine d. hôp. de Paris*, 1931, vii, 56.
27. KLING, K. G.: Malignant cranial chordoma; case, *Acta path. et microbiol. Scandinav.*, 1933, xvi, 194-203.
28. TRAINA, S.: Malignant chordoma of nasopharyngeal cavity, *Minerva med.*, 1934, ii, 83-89.
29. HAAS, G. M.: Chordoma of cranium and cervical portion of spine; review of literature with report of case, *Arch. Neurol. and Psychiat.*, 1934, xxxii, 300-327.
30. CAMAUER, A. F., and SACON, J. I.: Unilateral paralysis of nerves of base of cranium due to chordoma of physaliform synchondrosis (Guillain-Garcin syndrome), *Rev. Asoc. méd. argent.*, 1934, xlviii, 1251-1256.
31. HARBITZ, F.: Tumors arising from hypophyseal duct and other neoplasms related thereto, chordomas, *Acta path. et microbiol. Scandinav.*, 1935, xii, 38-78.
32. LIVINGSTON, G.: Chordoma of base of skull, *Proc. Roy. Soc. Med.*, 1935, xxvii, 1427-1429.
33. FURLOW, L. T.: Intracranial chordoma; case, *Arch. Neurol. and Psychiat.*, 1935, xxxiv, 839-843.
34. ADSON, A. W., KERNOHAN, J. W., and WOLTMAN, H. W.: Cranial and cervical chordomas; clinical and histologic study, *Arch. Neurol. and Psychiat.*, 1935, xxxiii, 247-261.
35. VAN WAGENEN, W. P.: Chordoblastoma of basilar plate of skull and ecchordosis physaliphora sphenoccipitalis; suggestions for diagnosis and surgical treatment, *Arch. Neurol. and Psychiat.*, 1935, xxxiv, 548-563.
36. FIDLOVOSKY, I. Y.: Malignant cranial chordoma; case, *Vrach. delo.*, 1935, xviii, 871-874.
37. CUSENZA, G.: Craniopharyngeal chordoma; clinical and anatomicopathologic study of case, *Oto-rino-laring. ital.*, 1936, vi, 421-433.
38. STEVENSON, L. D., and FRIEDMAN, E. D.: Chordoma involving ventral aspect of pons and medulla; two cases, *Brain*, 1936, lix, 291-301.
39. GOULD, S. E.: Spheno-occipital chordoma; report of case, *Arch. Otolaryngol.*, 1936, xxiii, 588-592.
40. BOEMKE, F., and JOEST, W.: Cranial chordoma, *Virchow's Arch. f. path. Anat.*, 1936, ccxcvii, 351-367.
41. GUTIERREZ, A., and MONSERRAT, J. L.: Chordoma of nasopharynx, case, *Rev. de cir. de Buenos Aires*, 1936, xv, 61-80.
42. ARGAUD, GORSE, and CALMETTE: Intra-orbital chordoma in child three years old, *Ann. d'anat. path.*, 1937, xiv, 419-422.
43. BRAITENBERG, H. VON: Zur Kenntnis der Basilar- und Sakralchordome, *Frankfurt Ztschr. f. Path.*, 1936-1937, i, 509-533.
44. DICKSON, W. E. C., WORSTER-DROUGHT, C., and McMENEMEY, W. H.: Spheno-occipital chordoma; case, *Jr. Path. and Bact.*, 1937, xlv, 41-46.
45. HRYNKIEWICZ, S.: Review of literature, with report of case of chordoma, *Polska gaz. lek.*, 1937, xvi, 849-953.
46. ROCHE, T., and MARTIN, J. F.: Ophthalmologic symptoms and lesions in patient with chordoma of sphenoidal origin; case, *Bull. et mém. Soc. franç. d'ophth.*, 1937, I, 70-79.
47. SZEKER, J.: Chordoma of nasopharynx; surgical therapy of case, *Monatschr. f. Ohrenh.*, 1937, lxxi, 1436-1444.
48. PEERS, J. H.: Spheno-occipital chordoma, *Am. Jr. Cancer*, 1938, xxxii, 221-226.
49. RIDPATH, R. F.: Chordoma, with report of two cases, *Ann. Otol., Rhin. and Laryng.*, 1938, xlvii, 649-658.
50. SCHNEEGANS, E., and MANDIGAS: Non-communicating hydrocephalus due to malignant chordoma; fatal case, *Bull. Soc. pediat. de Paris*, 1938, xxxvi, 535-538.

51. CALAMANDRAI, G.: Fine structure of benign chordoma of clivus, *Arch. ital. di med. sper.*, 1938, iii, 637-658.
52. REMAGGI, P. F.: Chordoma of clivus, *Oto-rino-laring. ital.*, 1939, ix, 209-219.
53. ZAMBRINI, A. R., and CASTELLANOS, F. J.: Chordoma of cavum, *Rev. Asoc. méd. argent.*, 1939, liii, 382-384.
54. MOLLER, H. U.: Symptoms presenting aspect of glaucoma in patient with chordoma of Blumenbach's clivus, *Acta ophth.*, 1939, xvii, 20-27.
55. ZEITLIN, H., and LEVINSON, S. A.: Intracranial chordoma, *Arch. Neurol. and Psychiat.*, 1941, xlv, 984-991.
56. BOLDREY, E., and McNALLY, W. J.: Chordoma of basiocciput and basisphenoid; four cases, *Arch. Otolaryng.*, 1941, xxxiii, 391-400.
57. GARDNER, W. J., and TURNER, O.: Cranial chordomas; clinical and pathologic study, *Arch. Surg.*, 1941, xlii, 411-425.
58. GRANDCLAUDE, C., DRESSENS, J., and TISON, P.: Sacrococcygeal chordoma, *Echo méd. du nord*, 1933, xxxvii, 186-189.
59. CARDENAS PUPO, M.D., and CALVO TARAFIA, I.: Aportacion a la histopatologia del chordoma, *Arch. de med. int.*, Habana, 1935, i, 439-462.
60. FLETCHER, E. M., WOLTMAN, H. W., and ADSON, A. W.: Sacrococcygeal chordomas; clinical and pathologic study, *Arch. Neurol. and Psychiat.*, 1935, xxxiii, 283-299.
61. ROCHE, THIERS, and MARTIN, J. F.: Ophthalmologic symptoms and lesions in patient with chordoma of sphenoidal origin; case, *Bull. et mém. Soc. franç. d'opht.*, 1937, 1, 70-79.
62. SCHWARTZ, G., KUHLMANN, J., and NADAUD, P.: Influence de la radiotherapie sur un epithelioma chordal, *Bull. Soc. radiol. méd. France*, 1936, xxiv, 748.
63. HARMOS, O., and PALMER, L. A.: Chordomata and report of case, *Virginia Med. Month.*, 1935-1936, lxii, 638-648.
64. HSIEH, C. K., and HSIEH, H. H.: Roentgenologic study of sacrococcygeal chordoma, *Radiology*, 1936, xxvii, 101-108.
65. GABRIEL, W. B.: Sacrococcygeal chordoma; case, *Proc. Roy. Soc. Med.*, 1936, xxix, 1007-1008.
66. SIMONDS, S.: Two specimens of chordoma of the sacrum, *West London Med. Jr.*, 1936-1937, xli, 57-58.
67. CAZZAMALI, P.: Central sacral chordoma; histogenetic, anatomicropathologic and clinical study of case, *Arch. ital. di chir.*, 1937, xlv, 175-199.
68. SCHWYZER, A.: Case of chordoma with a hitherto unobserved intraspinal extension, *Minnesota Med.*, 1937, xx, 15-21.
69. NASH, I. E., and LASKEY, N. F.: Sacrococcygeal chordoma; report of unusual case with especial reference to x-ray findings, *Jr. Urol.*, 1937, xxxviii, 81-90.
70. BARNES, V. D., and OWEN, S. E.: Chordoma: a case with unusual endocrine findings, *Am. Jr. Cancer*, 1937, xxix, 541-545.
71. COLEY, B. L.: Sacral chordoma; one year after radical excision, *Ann. Surg.*, 1937, cv, 463-466.
72. GHAREEB, A. A.: Two sacrococcygeal cases, *Jr. Egyptian Med. Assoc.*, 1938, xxi, 606-613.
73. RUCKENSTEIMER, E.: Sacrococcygeal chordoma, case with recovery persisting six years after roentgenotherapy, *Arch. ital. di chir.*, 1938, liv, 412-418.
74. BOBBIO, L.: Sacrococcygeal chordoma, clinical study of case, *Bull. e mém. Soc. piemontese di chir.*, 1938, viii, 4-9.
75. NAGASE, K.: Sacrococcygeal chordoma, case, *Gann.*, 1938, xxxii, 146-147.
76. ASHOUR, M. A.: Chordoma of anterior aspect of larynx and of sacrococcygeal region, two cases, *Jr. Egyptian Med. Assoc.*, 1939, xxii, 163-166.
77. LYALL, A.: Case in sacrococcygeal region, *Glasgow Med. Jr.*, 1939, cxxxi, 171-172.



78. MIXTER, C. G., and MIXTER, W. J.: Surgical management of sacrococcygeal and vertebral chordoma, *Arch. Surg.*, 1940, xli, 408-421.
79. BOWERS, W. F.: Sacrococcygeal chordoma, case, *Nebraska Med. Jr.*, 1940, xxv, 341-342.
80. HERMANN, G., and TOURNEAUX, F.: Les vestiges du segment caudal de la moelle épinière et leur rôle dans la formation de certaines tumeurs sacro-coccygiennes, *Compt.- rend. Acad. d. sc.*, 1887, civ, 1324-1326.
81. KLEBS, E.: Ein Fall von Ecchondrosis spheno-occipitalis amylacea, *Virchow's Arch. f. path. Anat.*, 1864, xxxi, 396.
82. ANDLER, R.: Die Klinik des sacrococcygealen Chordoma, *Arch. klin. Chir.*, 1926, cxliii, 467-490.
83. DOWLING, E., and SEPICH, M. J.: Of lumbar region as etiologic factor in development of syndrome of compression of caudaequina, *Rev. de especialid.*, 1928, iii, 149-175.
84. HUTTON, A. J., and YOUNG, A.: Chordoma; report of two cases; malignant sacrococcygeal chordoma and a chordoma of the dorsal spine, *Surg., Gynec., and Obst.*, 1929, cccxxxiv, 48-333.
85. HERRMANN, A.: Clinic and diagnosis of various cranial chordoma, *Arch. f. Ohren-, Nasen- u. Kehlkopfh.*, 1929, cxxiv, 127, 135.
86. ROCHER, H. L., and GUERIN, R.: Chordome de la nuque; extirpation, radiotherapie postoperative, mort; evolution totale en un an., *Soc. nat. de chir.*, 1930, lvi, 286.
87. HARBITZ, F.: Tumors originating from cranio-pharyngeal canal and related tumors, *Norsk. mag. f. laegevidensk.*, 1934, xcv, 785-812.
88. ELLIS, V. H.: Notochordal tumor of cauda equina in child of 8 years, *Brit. Jr. Surg.*, 1935, xxiii, 25-29.
89. OHEIN, L.: Malignant central chordoma of lumbar portion of spine, *Beitr. z. path. Anat. u. z. allg. Path.*, 1936, xcvi, 426-430.
90. ALBERT, B.: Of posterior mediastinum; two-stage operation, *Časop. lék česk.*, 1936, lxxv, 1347-1348.
91. Cabot Case 23281: Chordoma of second lumbar vertebra, *New England Jr. Med.*, 1937, ccxvii, 104-107.
92. BERTONI, G., and FRATINI, G. P.: Intradural chordoma of cervical spine causing spinal cord depression, *Arch. ital. di chir.*, 1938, I, 345-366.
93. GÜTHERT, H.: Chordoma of vertebral column, with report of case, *Ztschr. f. Krebsforsch.*, 1939, xlviii, 557-575.
94. RICHARDS, V., and KING, D.: Chordoma, *Surgery*, 1940, viii, 409-423.
95. LANDIVAR, A. F.: Of lower jaw; recovery after surgical therapy, *Bol. y trab., Soc. de cir. de Buenos Aires*, 1934, xviii, 443-453.

---

## THE DIAGNOSIS AND TREATMENT OF CONGENITAL HEMOLYTIC (SPHEROCYTIC) JAUNDICE: REPORT OF A CASE WITH UNUSUAL BLOOD FINDINGS ALTERED BY LIVER THERAPY \*

By HENRY B. SUTTON, M.D., F.A.C.S., and NORMAN S. MOORE, M.D., F.A.C.P.,  
*Ithaca, New York*

CONGENITAL hemolytic jaundice is a chronic blood dyscrasia generally characterized by microcytic anemia, acholuric jaundice, increased fragility of the red blood corpuscles to hypotonic salt solution, reticulocytosis, splenomegaly, and

\* Received for publication September 3, 1942.

From the Department of Clinical Medicine, Cornell University, Ithaca, New York.

crises of hemolysis. It has frequently been stated that the victims are more jaundiced than ill. The belief that it follows a benign course, compatible with active and long life except when hemolytic crisis occurs, has been widely accepted. Many cases, however, do not follow this benign pattern.<sup>1, 2, 3, 4, 25, 33, 36, 38</sup> There is an increasing disposition to emphasize the more severe aspects of this disease<sup>1, 2, 5, 33, 38</sup>; and there is a changing attitude toward therapy, particularly toward blood transfusions<sup>2, 5, 6, 29</sup> and splenectomy.<sup>1, 3, 4, 5</sup>

The classification of many cases is difficult. The subdivision of idiopathic hemolytic jaundice into a congenital and an acquired type is not entirely satisfactory, since there is no agreement on the criteria to be used in making this separation. There are a number of observers who regard these two generally accepted types of the disease as clinical variations of the same entity.<sup>4, 7, 8, 9, 10</sup>

Many times an error in diagnosis occurs when symptoms of the disease are present. This is particularly true in children. The fact that the blood findings vary during short time intervals in the same case makes both diagnosis and classification difficult.

Our purpose is to report a case of congenital hemolytic jaundice exhibiting an initial macrocytic blood picture with normal fragility of the red blood cells and total absence of reticulocytes, and acute abdominal symptoms, in which the blood, after liver therapy, showed many microcytes and an increased fragility.

We also discuss this case and the literature with special reference to classification, diagnosis, blood picture after liver therapy, transfusion, and splenectomy. No attempt has been made to summarize the literature nor to harmonize that part discussed. It is too voluminous to permit the former and too conflicting and contradictory to permit the latter.

#### CASE REPORT

The patient, a male, 21 years of age, was admitted to the Cornell University Infirmary one evening, after experiencing malaise, loss of appetite and energy for several days. Twelve hours before admission he had experienced initial severe pain in the left flank radiating around to the epigastrium, had felt "all in," and had passed several loose stools. The pain had been constant and consistently aggravated by movement. There had been no urinary symptoms.

For the previous two months he had experienced palpitation and shortness of breath on exertion, was easily fatigued, bothered by lack of concentration, and a tendency to worry. He had experienced one previous episode similar but not so severe, during January of 1939. At that time he had been confined to another hospital for three months and treated there solely for anemia. The hospital record showed that the hemoglobin had been reduced to 68 per cent and the red blood count to 1,900,000. The white blood count had been normal. No further investigations had been made. He had been given three transfusions with some improvement. No mention was recorded of adverse reactions to these. A definite diagnosis had not been made.

Diphtheria at three months and measles at the age of five years were the only illnesses previously encountered by the patient. Growth and development had followed a normal curve. The family history revealed that no analogous situations had occurred in the family. Mother, father, one sister, and a half brother were alive and well.

Physical examination revealed a well developed, fairly well nourished young male 21 years of age, obviously suffering severe pain. The skin and mucous mem-

branes were pale. There was no edema. The throat was slightly red. The cervical, axillary, and inguinal lymph nodes were palpable, discrete, slightly enlarged and tender. Examination of the chest was negative. Blood pressure (systolic) was 120 mm. Hg. There was tenderness in the left costovertebral angle extending around to the epigastrium and to the left upper quadrant where the muscles were so rigid that no intra-abdominal organs could be palpated. The white cells numbered 6,050; polymorphonuclears 66 per cent, lymphocytes 31 per cent, monocytes 3 per cent. The

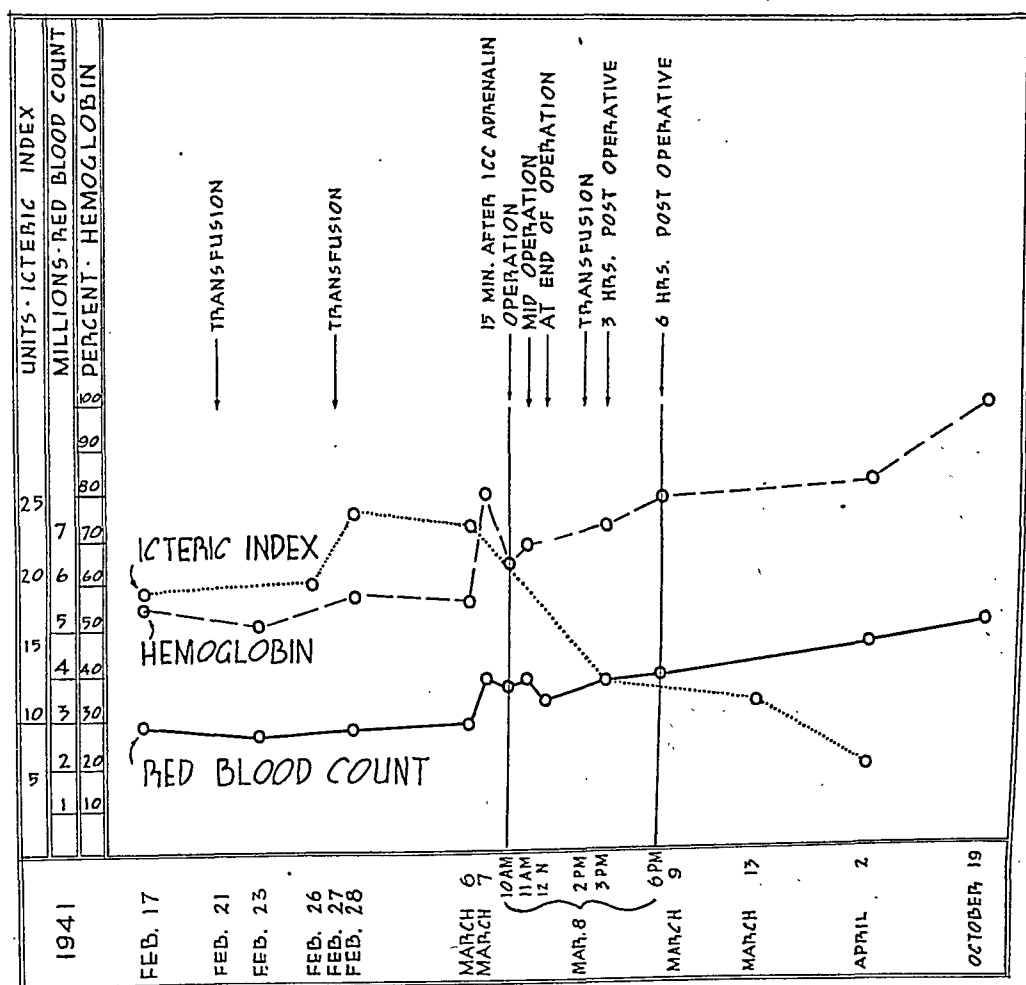


FIG. 1.

urine showed a slight trace of albumin. The temperature was 99, the pulse 88, and respirations 16. It was thought he might have the grippe.

In daylight next morning an icteroid tint was discernible. The blood then showed hemoglobin 61 per cent, red blood cells 2,820,000; CI 1.09; platelets 270,000; white blood cells 6,900; polymorphonuclears 59 per cent, lymphocytes 37 per cent, monocytes 2 per cent, eosinophiles 1 per cent. The icterus index was 21 units. The urine contained no bile, but urobilin was present. The peripheral blood showed no spherocytes. The blood smear closely resembled that of pernicious anemia. Many macrocytes and a few microcytes were present. There was a total absence of reticulocytes. The fragility test was equivocal, hemolysis beginning at .48 per cent saline, and was complete at .38 per cent (control range was from .46 per cent to .36 per cent

saline). It was at the time considered normal. Because of the blood picture, intensive liver therapy (1 c.c. concentrated extract intramuscularly daily) was administered for two weeks, but the anemia did not improve (figure 1). After the liver therapy there was, however, a striking change in the red blood cells and the fragility test. Many spherocytes appeared. The fragility range of the red blood cells changed to .50 per cent-.44 per cent saline (control .46 per cent-.30 per cent) and reticulocytes increased to 9.5 per cent. The icteric index was 19. Hemoglobin dropped to 53 per cent. The red blood count (2,790,000) remained at the previous level. Sternal puncture showed a normoblastic marrow. Gastric analysis revealed a total acidity of 4 units and a free HCl content of 2.8 units. Abdominal tenderness and rigidity had subsided during this time so that a mass in the left upper quadrant reaching almost to the umbilicus could be palpated. This was thought to be the spleen, and a diagnosis of chronic hemolytic jaundice of familial type in hemolytic crisis was made.

We were aware that severe reactions sometimes follow transfusions in these cases. Therefore, a small test transfusion was given without severe reaction and also without benefit. Indeed, 24 hours later the hemoglobin had decreased from 55 per cent to 53 per cent (figure 1) and the abdominal discomfort in the region of the spleen had increased. After one week had passed a larger transfusion (500 c.c.) was given. Twenty-four hours later the hemoglobin and red cells were slightly higher but the icteric index had risen from 20 to 26 units (figure 1). Abdominal discomfort had increased. We suspected that the transfusions had increased the hemolysis and that they had made the patient clinically worse.

Though it was recognized that the hemolytic crisis continued, immediate splenectomy was decided upon in lieu of further medical treatment. The patient had improved objectively and subjectively, but little improvement in the blood findings had occurred. The hemoglobin was 60 per cent; the red blood count was 3,020,000; and the icteric index was 24. To ascertain what improvement could be expected from the autotransfusion incident to the emptying of the spleen, a blood count was made 15 minutes after the intramuscular injection of 1 c.c. of adrenalin. The hemoglobin rose to 80 per cent and the red blood count to 3,870,000. Splenectomy was done without great difficulty on March 8. The spleen removed weighed 2178 grams. The gall-bladder was found to contain many small stones but was not disturbed. There were no accessory spleens. Dr. Henry Ferris, pathologist, reported "splenomegaly with intense congestion."

Blood studies made before, during, and after splenectomy showed striking changes. The preoperative hemoglobin was 61 per cent, red blood cells were 3,030,000. The icteric index was 24. A count taken at mid-operation showed the hemoglobin to be 68 per cent and red blood cells to number 4,000,000. At the end of the operation the hemoglobin was 70 per cent and the red blood count was 3,440,000. Three hours after splenectomy the hemoglobin was 77 per cent and the red blood count was 3,800,000. Six hours after the operation the hemoglobin had risen to 79 per cent and the red blood count to 3,900,000. Twenty-four hours after the operation the hemoglobin was 78 per cent and the red blood cells numbered 3,870,000. The icteric index was 12 units.

These findings corroborate the observations of Doan, Curtis, and Wiseman,<sup>1, 3</sup> both as to the rapid increase in red cells and hemoglobin during and after the operation as well as the rapid fall in the icteric index, the latter indicating a rapid decline in the rate of hemolysis. Sharpe<sup>37</sup> concludes that this immediate effect on hemoglobin and red blood cells is temporary and due solely to the autotransfusion incident to the emptying of the spleen.

Several hours after the operation the patient was given a transfusion for secondary shock from which recovery was prompt without adverse reaction. His con-

valescence was uneventful except for rather severe, protracted epigastric pain accompanied by some nausea and vomiting. This was attributed to gall-stones which were known to exist. His wound healed by primary union. He was discharged on April 16, the forty-third postoperative day. On that day the hemoglobin was 80 per cent and the red blood cells numbered 4,090,000. He was reëxamined October 19, 1941 and found to be in excellent condition, having gained 15 pounds in weight and having no subjective complaints. He was working as a truck driver, which required heavy lifting. He had experienced no palpitation or dyspnea, nor had he suffered any attack of abdominal pain. He did not tire easily. Difficulty in concentration was less evident. No retardation was noticeable. A blood examination showed the hemoglobin to be 102 per cent; the red blood cells to number 4,780,000; the white blood count to be 17,950; polymorphonuclears 76 per cent, lymphocytes 17 per cent, monocytes 4 per cent, eosinophiles 2 per cent, basophiles 1 per cent. The range of hemolysis of the red cells was from .48 per cent to .32 per cent saline. Many spherocytes (estimated 50 per cent) were present. There was a total absence of reticulocytes. The elevated white blood count was in part caused by contusions received in an automobile accident one day before the count. We considered him to be an example of cure following splenectomy. A letter from this patient received April 1, 1942 informed us that he had been accepted by the United States Army for military service.

We wish to emphasize the following features of this case and to discuss them with reference to the literature: (1) Classification and diagnosis; (2) the effect of liver therapy on the blood picture; (3) the fragility test; (4) reticulocytosis; (5) the effect of transfusions; (6) splenectomy.

#### CLASSIFICATION AND DIAGNOSIS

The hemolytic anemias cover a number of conditions which have been variously grouped and named. There is considerable variation in the designation of these diseases and some disagreement on classification. Although there is considerable disposition to regard the familial and idiopathic acquired type as variations of the same disease,<sup>4, 7, 8, 9, 10</sup> some authorities<sup>40</sup> still retain the old division into the congenital (Chaufford-Minkowski) type and the acquired (Hayem-Widal) type. The more recent suggestion of Thompson<sup>12</sup> to divide them into "spherocytic" and "the atypical type" is gaining adherents. The condition so long known as congenital or familial hemolytic jaundice in which the familial factor may be entirely masked or absent corresponds rather closely to Thompson's spherocytic jaundice, but there are discrepancies.

The diagnosis in children may be particularly difficult where, according to Debre et al.,<sup>36</sup> icterus and increased fragility are often lacking. Anemia is also sometimes absent. They point out that splenomegaly is the only constant feature. The fact that the blood picture varies in the same case at different times as in the case here reported makes diagnosis and classification in certain instances difficult. Riddle, in discussing Hill's work,<sup>35</sup> emphasizes this point. There also may be variation in any, or all, of the other symptoms, none of which is invariably observed.<sup>20, 39</sup> Pemberton<sup>11</sup> reports that Giffin at the Mayo Clinic found that 23 of 118 cases had been operated on for complicating gallstones before the diagnosis of primary hemolytic jaundice had been made.

Although we can discover no familial background, we believe that our case should be classified as one of congenital hemolytic jaundice. It also fits into Thompson's classification of "spherocytic anemia."

The spherocyte which is the basis of Thompson's classification was first described by Naegeli<sup>14</sup> who believed it to be pathognomonic of congenital hemolytic jaundice. Gaensslen<sup>15</sup> correlated the spherical nature of the cells with increased fragility, and Haden<sup>16</sup> considers that all other manifestations of the disease are secondary to the spherocytic nature of the red cells and that the primary defect is in the bone marrow. Meulengracht<sup>40</sup> does not agree with Gaensslen and cites cases with increased fragility of the red blood cells in which the red cell diameters are greater than normal (8.2 microns).

Thompson's impressions may be summarized as follows: Spherocytic jaundice is a uniform disease entity; the spherocytes are pathognomonic and take an active part in the disease process. All patients with spherocytic jaundice have spherical microcytes in their blood. These cells are directly responsible for the fragility in hypotonic salt solution. The cells of the blood are selectively removed from the general circulation in the spleen where they are found in greater numbers than in the peripheral blood. There is enough evidence to warrant the assumption that all the increased red blood cell destruction that occurs during the hemolytic phase takes place in the spleen. Diagnosis of the disease is possible from microscopic sections of the spleen alone, for the pathologic histology is specific. The symptoms of spherocytic jaundice are promptly, completely, and permanently relieved by splenectomy, although the spherical cells with their attendant fragility changes persist.

There are undoubtedly many cases like the one here presented that do not meet all of Thompson's requirements but are, however, in most particulars, identical with spherocytic anemia. Some cases with normal fragility and no spherocytes respond to splenectomy and behave as do the true spherocytic anemias. Other cases with spherocytes and increased fragility do not behave as spherocytic anemias and do not respond to splenectomy. There are instances in which the presence of spherocytes is not attended by increased fragility and also cases reported in which macrocytic blood shows increased fragility.<sup>40</sup> Dameshek<sup>17</sup> has had two cases of spherocytic jaundice which have failed to respond to splenectomy and one case in which the spherocytes and increased fragility disappeared after splenectomy. Hill<sup>35</sup> also cites cases in which these findings have disappeared after splenectomy. Dameshek<sup>17</sup> produces spherocytes and increased fragility experimentally by the injections of hemolytic agents. Van Boros<sup>18</sup> and Heilmeyer<sup>19</sup> have found spherocytes and increased fragility in other conditions. It is apparent, as Hanrahan and Vincent<sup>20</sup> point out, that the designation of these cases does not lend itself kindly to over-simplification.

#### THE BLOOD PICTURE AND LIVER THERAPY

The initial blood picture in our case presented several unusual features: (1) a macrocytosis, anisocytosis, and poikilocytosis, (2) a lack of spherocytes with normal fragility, and (3) an absence of reticulocytes. The original smear and wet preparation seemed quite like those of pernicious anemia. Therefore, one c.c. of concentrated liver extract was given intramuscularly daily for two weeks. At the end of this period many spherocytes were observed and the fragility of the

red blood cells to hypotonic saline had increased. There are several cases reported<sup>35</sup> in which this change has taken place in the blood picture. One case is detailed by Riddle<sup>35</sup> in which the blood picture was followed through several changes. In the first phase the blood picture was that described as typical of familial jaundice. Some time later the blood presented a leukemoid picture with 40,000 white cells, many of which were myeloid in type and still later the blood picture was indistinguishable from that of pernicious anemia with macrocytosis, etc. The blood picture then reverted to the original one under liver therapy. Hill explains this macrocytic picture by assuming that during the long continued and excessive demand incident to increased erythropoiesis which exists in these cases the erythrocytic maturing factor is depleted. The supplying of this factor allows normal maturation of the red cells. This is especially apt to occur if cirrhosis or other damage to the liver exists.

Although it is true that liver therapy as a therapeutic measure to combat the anemia is generally considered useless and is said in certain instances to increase the hemolysis, it served a useful purpose in this case by producing a rapid change in the blood picture, thus lending material aid in the diagnosis. When blood pictures are atypical its use is justified on this basis alone. Reifenstein<sup>21</sup> feels that further study should be made before definite conclusions can be drawn regarding the efficiency of liver therapy.

#### THE FRAGILITY TEST

An increased fragility of the red blood cells to hypotonic salt solution is said by certain observers to be pathognomonic of hemolytic jaundice. Dawson<sup>2</sup> states that the fragility is not altered in 10 per cent of the cases and others deny that it is a prerequisite to diagnosis. It is conceded to be an important diagnostic aid. These tests in our case showed little variation. In the initial test with a macrocytic blood, hemolysis began at .48 per cent saline and began in the control at .46 per cent, a difference of only .02 per cent. After liver therapy when spherocytes were present, hemolysis began at .50 per cent and began in the control at .46 per cent, a difference of .04 per cent. The first test was interpreted as normal and the second as showing a decreased resistance. After splenectomy hemolysis appeared again in .48 per cent saline and in the control in a .46 per cent solution. At this time there were many spherocytes present.

It is evident that a test which is as important as the fragility test is thought to be, should be carefully controlled; yet we find controls rarely mentioned in the literature. In a series of cases Watson<sup>32</sup> found that hemolysis in normal controls began in concentrations of saline varying between .54 per cent and .38 per cent. The finding of such wide variation in normal controls makes it difficult to interpret such small differences as .02 per cent and .04 per cent between beginning hemolysis of the patient's blood and that of the control. Such difficulty existed in our case.

From these figures and the variation of those reported elsewhere, it seems reasonable to question the reliability of the test as it is usually done. We doubt if it is reliable enough to be dependable as a major diagnostic point.

Doan, Wiseman, and Erf,<sup>22</sup> after critical analysis, conclude that fragility tests done with hypotonic saline are universally unsatisfactory even under the best controlled conditions. If a test were accurate, we should expect less divergent

results in normal controls. Wiseman and Bierbaum<sup>23</sup> have devised and described a test using distilled water instead of saline which seems more accurate. There is almost no variation exhibited among normal controls in the point at which hemolysis begins. The value is almost constant. They express their results in saline equivalents, the normal limits being 0.300 to 0.412 per cent. These limits thus sharply defined have been found so generally under normal conditions that any deviation in either direction may be interpreted as an abnormality. The only control necessary is a specimen of the patient's whole blood to be certain that no hemolysis has occurred in the collection of the specimen. The information we really want when we do a fragility test is the degree of stability of the red cells of a given patient in that patient's own serum. Their test seems to give this information.

The following statements concerning the red cell fragility seem justified: (1) the fragility in hemolytic icterus varies in different subjects; (2) it varies in the same individual at different times; (3) an increased fragility is the usual finding but it is not necessary in order to make the diagnosis; (4) it is not pathognomonic of the disease when it is present.

### RETICULOCYTOSIS

Reticulocytosis is said to be a prominent feature of the blood picture in hemolytic jaundice. It is considered to be of important diagnostic significance.<sup>18</sup> In general the more active the hemolytic process, the higher the reticulocytosis.<sup>18</sup> It may even be so pronounced that it dominates the blood picture. It has been said that the fluctuations in the disease may be followed by the rise and fall of the reticulocyte counts. Although the average is between 20 per cent and 30 per cent,<sup>12</sup> a count above 50 per cent is not unusual. Baty<sup>24</sup> reports a patient in whom the reticulocytes reached 92 per cent, and Reynolds<sup>25</sup> one whose reticulocytes reached 95 per cent. Tileston<sup>24</sup> states that reticulocytosis exists to a far greater degree than found in any other disease. Vital staining in our patient revealed an initial total absence of reticulocytes, and only 9.5 per cent were found after liver therapy. It is interesting to note that a number of normal reticulocyte counts<sup>26, 27, 28</sup> are recorded but we found the report of no case which presented a total absence of these cells.

### TRANSFUSIONS

It would be quite natural to assume that the treatment for a chronic disease marked by anemia, oftentimes rapidly progressive, not responding to iron, arsenic, or liver, would be transfusion or repeated transfusion. Although many authors do not mention it, an increasing number<sup>1, 2, 5, 6, 13, 29, 30</sup> are not only impressed by the lack of benefit derived from transfusions but they point out that increased hemolysis and aggravation of clinical symptoms often follow, and also that in certain cases even death may ensue. In our case the patient was given three transfusions (figure 1) all from the same donor whose blood was of the same type. The first or "pilot" transfusion of 200 c.c. was followed by slight aggravation of abdominal discomfort and a definite fall in the hemoglobin (figure 1). After the second larger transfusion (500 c.c.) there was even more increase in abdominal pain and some elevation of heart rate. Although there was a slight



gain in hemoglobin and red blood cells at the end of 24 hours, the icteric index had risen from 20 to 26 units indicating an increased hemolysis. There was no evidence of any reaction when 450 c.c. of blood were given to him six hours after splenectomy.

Baker and Dodds<sup>6</sup> record a fatal case in which several transfusions had been given, followed each time by high temperature, nausea and vomiting, and deepening jaundice. Autopsy revealed the kidney tubules blocked by acid hematin. Dawson of Penn<sup>2</sup> warns of the danger. Dameshek<sup>13</sup> mentions several reactions following the use of a donor of the same type as the recipient. Doan<sup>5</sup> is emphatic in his statements concerning the dangers of transfusion, and the fourteenth edition of Osler<sup>30</sup> mentions it. Some conclude that transfusion is contraindicated. Kilduffe and De Bakey<sup>31</sup> feel that severe reactions are unusual but that preserved blood should not be used. Our experience with this case and a perusal of the literature lead us to believe that the profession in general does not yet appreciate the grave dangers that may accompany transfusions in hemolytic jaundice. We advocate extreme caution and suggest a small "pilot" transfusion as advised by Dawson.<sup>2</sup>

#### SPLENECTOMY

Although splenectomy is the accepted method of treatment and is said to be regularly curative in a clinical sense, there was until recently all but universal agreement that the operation should not be done during a hemolytic crisis. However, an occasional death occurs before remission from hemolytic crisis in spite of all other treatment.<sup>2, 36, 38</sup> In cases like this, it is the contention of Doan, Curtis, and Wiseman<sup>1, 3</sup> that not only is splenectomy desirable but an emergency splenectomy is imperative. They report five cases of congenital hemolytic jaundice in acute fulminating crisis with red cells at or below 1,000,000 in which splenectomy was carried out. There were no fatalities and in each case there was a dramatic rise in the hemoglobin and red blood cells while the patient was still on the table. There was an immediate cessation of hemolysis. This immediate and striking improvement occurred in every case. They feel it can be relied upon and that splenectomy under such circumstances is a life saving measure. In the case here reported, splenectomy was done during a hemolytic crisis and a dramatic effect on the blood picture and hemolysis (figure 1) was observed. Dameshek and Schwartz<sup>13</sup> also advocated emergency splenectomy in certain cases of acute acquired hemolytic anemia (Lederer's anemia), a type which has been accepted as one which usually responds dramatically and permanently to transfusions. Debre<sup>36</sup> advocates splenectomy in infants and children before puberty because the disease may produce infantilism, skeletal deformities and mongoloid features in these patients. Krumbhaar<sup>7</sup> feels that the advice to operate during crisis without waiting for remission or benefit of transfusion should be followed with caution and reluctance. It seems reasonable, nevertheless, to admit that our ideas concerning splenectomy during a crisis in either the congenital or acquired type of hemolytic jaundice may be in need of revision; and that in certain carefully selected cases splenectomy is not only advisable but positively indicated.

## SUMMARY

1. A case of hemolytic jaundice in hemolytic crisis is reported in which the blood exhibited a macrocytosis, normal fragility and total absence of reticulocytes at the time of initial examination of the red cells.
2. A spherocytic blood picture with increased fragility and 9.5 per cent reticulocytes appeared after liver therapy.
3. Splenectomy during a crisis was followed by an immediate dramatic rise in hemoglobin and red cells and an abrupt cessation of hemolysis.
4. Transfusions were cautiously given without severe reaction, but with definite signs of increased hemolysis.
5. A warning is sounded concerning transfusions in hemolytic jaundice.
6. Favorable opinion is expressed regarding "emergency splenectomy."

## BIBLIOGRAPHY

1. DOAN, C. A., CURTIS, G. M., and WISEMAN, B. K.: The hemolytotoxic equilibrium and emergency splenectomy, *Jr. Am. Med. Assoc.*, 1935, cv, 1567-1574.
2. DAWSON, B.: Hemolytic icterus—Hume Lecture, *Brit. Med. Jr.*, 1931, i, 921-928.
3. CURTIS, G. M., DOAN, C. A., and WISEMAN, B. K.: Splenectomy for hemoclastic crises, *Ann. Surg.*, 1936, civ, 892-904.
4. BRANCH, C. D.: Congenital hemolytic jaundice (spherocytic jaundice), *Illinois Med. Jr.*, 1941, lxxx, 235-238.
5. DOAN, C. A.: Hemolytic anemias, in BARR, D. P.: *Modern medical therapy in general practice*, 1940, Williams and Wilkins, Baltimore, iii, 2937.
6. BAKER, S. L., and DODDS, E. C.: Obstruction of renal tubules during excretion of hemoglobin, *Brit. Jr. Exper. Path.*, 1925, vi, 247-260.
7. CUSTER, R. P., and KRUMBHAR, E. B.: Hemolytic anemias, *Specialties in Medical Practice*, 1939, Thomas Nelson and Sons, New York, iv, Chapt. V, p. 35.
8. KRUMBHAR, E. B.: Modern concept of anemia from the clinical standpoint, *Bull. New York Acad. Med.*, 1937, xiii, 501-511.
9. VAUGHAN, JANET M.: *The anemias*, 1934, Oxford University Press, New York.
10. HURXTHAL, L. M.: Hemolytic jaundice, considerations in diagnoses and treatment, *Surg. Clin. N. Am.*, 1935, xv, 1475-1480.
11. PEMBERTON, J. DE J., and MAHORNER, H. R.: Congenital hemolytic icterus, *Surg. Clin. N. Am.*, 1931, xi, 787-793.
12. THOMPSON, W. P. (New York): Hemolytic jaundice: its diagnosis, behavior and treatment, *Bull. New York Acad. Med.*, 1939, xv, 177-187.
13. DAMESHEK, W., and SCHWARTZ, S. O.: Acute hemolytic anemia (acquired hemolytic icterus, acute type), *Medicine*, 1940, xix, 231-337.
14. NAEGELI, O.: *Blutkrankheiten und Blutdiagnostik*, Ed. 3, 1919, Walter de Gruyter, Berlin, p. 408.
15. GAENSSLEN, M.: Hemolytic icterus, *Deutsch. Arch. f. klin. Med.*, 1922, cxl, 210-226.
16. HADEN, R. L.: The mechanism of increased fragility of the red blood cells in congenital hemolytic jaundice, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 441-449. Nature of hemolytic icterus, Symposium on blood and blood forming organs, 1939, University of Wisconsin Press, Madison.
17. DAMESHEK, W., and SCHWARTZ, S. O.: Hemolysins as the cause of clinical and experimental hemolytic anemias, with particular reference to the nature of spherocytosis and increased fragility, *Am. Jr. Med. Sci.*, 1938, cxcvi, 769-792.
18. v. BOROS, J.: Ueber Grösse, Volumen und Form der menschlichen Erythrozyten und deren Zusammenhang. ii. Die Mikrozytose beim hämolytischen Ikterus, *Wien. Arch. f. inn. Med.*, 1926, xii, 255-272.

19. HEILMYER, L.: Die Spharocytose als Ausdruck eines pathologischen Funktion der Milz, *Deutsch. Arch. f. klin. Med.*, 1936, clxxix, 292-306.
20. HANRAHAN, E. M., and VINCENT, B.: *Lewis Surgery*, 1940, Wm. F. Prior, Hagerstown, Md., Vol. VI, Chapt. XV, p. 99.
21. REIFENSTEIN, E. C., and ALLEN, E. G.: The treatment of chronic hemolytic jaundice with liver extract, *Jr. Am. Med. Assoc.*, 1934, ciii, 1668-1671.
22. DOAN, C. A., WISEMAN, B. K., and ERF, L. A.: Studies in hemolytic jaundice, *Ohio State Med. Jr.*, 1934, xxx, 493-516.
23. WISEMAN, B. K., and BIERBAUM, O. S.: New method for determining fragility of red cells, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 835-838.
24. BATY, J. M.: Case of congenital hemolytic jaundice with unusual high percentage of reticulocytes, *Am. Jr. Med. Sci.*, 1930, clxxix, 546-549.
25. REYNOLDS, G. P.: Case of acquired hemolytic jaundice with unusual features and improved by splenectomy, *Am. Jr. Med. Sci.*, 1930, clxxix, 549-553.
26. VAUGHAN, J. M.: Red cell characteristics in acholuric jaundice, *Jr. Path. and Bact.*, 1937, xlv, 561-577.
27. HURLEY, A. G., and MOORE, W. C.: Congenital hemolytic jaundice. Report of case with normal fragility and normal reticulocyte count cured by splenectomy, *Ann. Surg.*, 1940, cxii, 392-399.
28. BIRCH, C. L., and JAFFE, R. H.: Chronic hemolytic icterus in adolescence, *Med. Clin. N. Am.*, 1928, xii, 255-269.
29. SHARP, J. C., and DAVIS, H. H.: Severe reactions following transfusions in hemolytic jaundice: report of two cases, *Jr. Am. Med. Assoc.*, 1938, cx, 2053-2056.
30. CHRISTIAN, H. A.: *Osler's principles and practice of medicine*, 13th Ed., 1938, D. Appleton-Century Company, New York, p. 909.
31. KILDUFFE, R. A., and DEBAKEY, M.: The blood bank, 1942, C. V. Mosby, St. Louis, p. 75.
32. WATSON, C. J.: Hemolytic jaundice and macrocytic hemolytic anemia: certain observations in a series of 35 cases, *Ann. Int. Med.*, 1939, xii, 1782-1796.
33. WISE, W. D.: Hemolytic jaundice, report of five splenectomies in one family, *Am. Jr. Surg.*, 1933, xx, 722-736.
34. TILESTON, W.: Hemolytic jaundice, *Medicine*, 1922, i, 355-388.
35. HILL, J. M. (Dallas, Texas): Dimensions of the red cells in familial hemolytic anemia with particular reference to atypical cases, *Jr. Am. Med. Assoc.*, 1938, cxi, 2179-2183.
36. DEBRE, R., LAMY, M., SEE, G., and SCHRAMECK, G.: Congenital and familial hemolytic disease in children, *Am. Jr. Dis. Child.*, 1938, lvi, 1189-1214.
37. SHARP, J. C., McLAUGHLIN, C. W., and CUNNINGHAM, R.: Hemolytic jaundice: immediate and delayed changes in the blood after splenectomy, *Arch. Int. Med.*, 1939, lxiv, 268-279.
38. SMITH, G. O.: Chronic hereditary hemolytic jaundice, *Jr. Am. Med. Assoc.*, 1935, cv, 1187-1188.
39. WEBER, F. P.: Case described as acholuric (hemolytic) jaundice in 1909. (Congenital acholuric jaundice, without anemia, splenomegaly or fragility of red corpuscles), *Proc. Roy. Soc. Med.*, 1938, xxxi, 555-556.
40. MEULENGRACHT, E.: Chronic hereditary hemolytic jaundice, *Handbook of Hematology*, 1938, P. B. Hoeber, New York, Sec. XXXI, p. 2216.

## ACUTE HEMOLYTIC ANEMIA WITH TOXIC HEPATITIS CAUSED BY SULFADIAZINE; REPORT OF A CASE\*

By DOUGLAS DONALD, M.D., F.A.C.P., and RICHARD E. WUNSCH, M.D.,  
*Detroit, Michigan*

ACUTE hemolytic anemia resulting from the use of sulfonamides has been frequently reported. Long, Haviland, Edwards and Bliss,<sup>1</sup> in a large series, noted its occurrence in 1.8 per cent of cases following the administration of sulfanilamide and in 0.6 per cent after sulfapyridine. This toxic effect was not seen with sulfathiazole.

Rothstein and Cohn,<sup>2</sup> however, have recently reported one case, and Bunim and Israel<sup>3</sup> two cases following sulfathiazole.

Sulfadiazine has been considered innocuous as far as the hematopoietic system is concerned. Mild anemias may occur, but to date no case of hemolytic anemia following its use has been reported. For this reason we believe it important to report the following case of acute hemolytic anemia and toxic hepatitis following the administration of sulfadiazine.

### CASE REPORT

E. P. W., a white male, age 47, was admitted to Harper Hospital on March 8, 1942 with a history of rhinorrhea, sore throat, generalized aching and malaise for one week. Twenty-four hours previous to admission he had a chill, sharp pain in left chest accentuated by respiration, cough productive of purulent, rusty sputum and nausea and vomiting. No chemotherapy had been attempted before admission.

Physical examination revealed an acutely ill patient, pale and dehydrated, temperature 103.4° F., respirations 36, pulse 132, blood pressure 68 mm. Hg systolic and 34 mm. diastolic. The pharynx was acutely injected; the chest showed dullness to percussion, tubular breathing, moist râles, and a pleural rub over the left base posteriorly and left axilla. Other positive findings included poor cardiac tones with a soft systolic murmur (this latter present over a number of years), and slight abdominal distention. Initial blood count: hemoglobin 92 per cent; red blood cells 4,450,000; white blood cells 11,000, with 89 per cent polymorphonuclears and 11 per cent lymphocytes. Sputum typing showed types III and V pneumococci on March 9, 1942. Sputum pneumococcus count (March 9, 1942—method of Drs. Price, Frisch, etc.<sup>4</sup>) showed s.s.s. reticular network, clumping with some phagocytosis and 10 organisms per high power field.

An admission diagnosis of left lower lobe pneumonia was made and patient given sodium sulfadiazine intravenously 2.5 gm. twice at two hour intervals on March 8, 1942, followed by sulfadiazine, 1.0 gm. orally at four hour intervals day and night with 10 gm. sodium bicarbonate with each dose.

Roentgenogram on March 10, 1942 confirmed the diagnosis of left lower lobe lobar pneumonia.

The clinical course showed slight improvement in 48 hours, an oxygen tent being used after the first 24 hours, but the temperature remained about 101° F., and on March 11, 1942, because of low drug levels, sulfadiazine was increased to 1.5 gm. every four hours and the patient was also given 80,000 units of type V antipneumococcic rabbit serum intravenously.

\* Received for publication June 29, 1942.

From the Medical Clinic of Harper Hospital, Detroit, Michigan.

On March 12, 1942 there was evidence of extension to the right base. Hemoglobin was 78 per cent; white blood cells numbered 13,500. On March 13, 1942, hemoglobin was 74 per cent; white blood cells numbered 14,850.

On March 14, 1942 the temperature had gradually dropped to 100° F., and sulfadiazine was reduced to 0.5 gm. every four hours. Hemoglobin was 69 per cent; white blood cells numbered 19,000.

Early on March 15, 1942 the temperature rose to 101° F., and it was felt that there was probably an extension of the process in the left lung. Therefore, sulfadiazine was increased to 1.5 gm. every four hours. By the following morning (March 16, 1942) the temperature was 103.6° F., and definite icterus was present. The liver was palpable and tender. The leukocyte count rose to 30,000; hemoglobin was 71 per cent. Sulfadiazine was stopped immediately. In eight days 59 gm. of the drug had been given, with blood levels ranging from 5.2 to 11.1. On March 16, 1942, the last day of treatment, the level was 10.7.

On March 17, 1942 the icteric index was 35; the Van den Bergh reaction was positive—direct and indirect.

Hemoglobin had dropped to 53 per cent, red blood cell count to 2,666,000, white blood cell count to 25,550. It was clear that a severe hemolytic anemia with toxic hepatitis had developed, and as with other sulfonamides, the hemolytic process was preceded by a sharp rise in leukocytes.

Blood transfusion was decided upon. The patient was found to be a type IV, and the department of hematology reported numerous cross agglutinations with potential donors of type IV, with the constant finding of agglutinations of the donor's cells by the patient's serum. It was finally decided that this phenomenon must be due to the presence of atypical agglutinins. Tests were then made for the so-called cold agglutinins. A suspension of the donor's cells in the recipient's serum was placed in the refrigerator with heavy agglutination resulting. The same suspension was then incubated at 37° C. for five minutes, with the result that the agglutination was completely broken up and a satisfactory reaction obtained. It was found that this process could be repeated at will by taking the same mixtures and alternately placing in the ice box and incubator. Furthermore, the same reaction occurred when the patient's cells and serum were mixed, indicating the presence of auto-agglutinins.

On March 17, 1942 transfusions were started and 250 c.c. of citrated blood were given on five occasions without reaction of any kind.

Other treatment consisted of fluids forced orally and parenterally, thiamine chloride 50 mg. intravenously, liver extract 1 c.c. intravenously and ferrous sulphate, 1 gm. by mouth daily. A high carbohydrate diet was administered.

The patient's course was stormy for several days, with increasing anemia. However, by March 24, 1942 improvement began, the icterus lessened and the blood picture improved. Temperature became normal on the eighteenth hospital day.

Subsequent blood studies were as follows: (3-19) Hemoglobin 34 per cent. Red blood cells 2,170,000. (3-20) Erythrocyte fragility: hemolysis began at .50 per cent, ended at .30 per cent. Reticulocyte count 4.5 per cent. (3-24) Hemoglobin 45 per cent. Red blood cells 2,340,000. (3-27) Hemoglobin 58 per cent. Red blood cells 2,890,000. (4-8) Icteric index 6. (4-13) Hemoglobin 77 per cent. Red blood cells 3,940,000.

The patient was discharged on April 13, 1942. Chest findings were entirely negative. Icterus had cleared and liver edge was no longer palpable. A slight anemia still existed.

#### SUMMARY

A case of acute hemolytic anemia with toxic hepatitis following the administration of sulfadiazine (59 gm. in eight days) is reported. To the best of our

knowledge there are no previous reports of this occurring, and for this reason we feel it important to call attention to this possible danger.

### BIBLIOGRAPHY

1. LONG, P. H., HAVILAND, J. W., EDWARDS, L. B., and BLISS, E. A.: Toxic manifestations of sulfanilamide and its derivatives, with reference to their importance in course of therapy, *Jr. Am. Med. Assoc.*, 1940, cxv, 364.
2. ROTHSTEIN, I., and COHN, S.: Acute hemolytic anemia, auto-agglutination, toxic hepatitis and renal damage following sulfathiazole therapy, case report, *Ann. Int. Med.*, 1942, xvi, 152-161.
3. BUNIM, J. J., and ISRAEL, M.: Acute hemolytic anemia caused by sulfathiazole, *Ann. Int. Med.*, 1942, xvi, 333-339.
4. PRICE, A. E., and FRISCH, A. W.: Sputum studies in pneumonia. The selection of therapy, *Ann. Int. Med.*, 1941, xv, 987-993.

---

## SPONTANEOUS PNEUMOTHORAX AND BRONCHIAL ASTHMA\*

By HUGO T. ENGELHARDT, M.D., and VINCENT J. DERBES, M.D.,  
*New Orleans, Louisiana*

THE increase in diagnostic acuity during the past few decades has demonstrated the fact that relatively few cases of spontaneous pneumothorax are due to tuberculosis. On the other hand, factors which cause increased intra-alveolar pressure and thinning of the alveolar wall are almost uniformly present in chronic asthmatic patients. One would then anticipate, a priori, that spontaneous pneumothorax would be a frequent complication in these individuals. An inquiry into the literature on this subject has failed to reveal more than 20 such instances, and, of this number, only two have been verified by autopsy (table 1).

Recently our attention has been directed to a case which presented the characteristics of this symptom complex.

### CASE REPORT

The patient was a 48 year old, white male, who entered the hospital on September 14, 1941, complaining of marked dyspnea of three weeks' duration. He stated that for about 20 years he had had a chronic productive cough. A year and one-half prior to entry he had been ill with pneumonia. Following this he had an attack of asthma which recurred three or four times subsequently. About three weeks before hospitalization he rather suddenly developed severe dyspnea and orthopnea. During the two weeks immediately preceding admission his feet and ankles had been swollen and he had lost several pounds in weight. There is no record of episodes of hemoptysis or chest pains. His family history and past history are irrelevant.

The physical examination revealed a poorly nourished, acutely ill patient, unable to breathe lying down. His temperature was 98.4° F., pulse 140, respirations 46, and blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The trachea was displaced

\* Received for publication December 18, 1942.

From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana, New Orleans, Louisiana.

to the left. Although the lungs expanded equally on the two sides, the respirations were shallow and labored. Over the right lung field there were hyperresonance, diminished tactile fremitus and diminished breath sounds. Moist râles were heard over the lower halves of both lung fields. The cardiac border was markedly displaced to the left and there was a systolic murmur over the pulmonic area. There was pitting edema of both feet and ankles.

TABLE I

Authors	Age of Patient	Sex	Duration of Asthma	Affected Side	Duration of Pneumothorax	Course	Results
Debove <sup>12</sup>	27	Male	Since infancy	Left	Few days	Without effusion	Cure
Emerson-Beeler <sup>12</sup>	22	Female	Twenty years	Bilateral	Six months	Without effusion	Death*
Spivake <sup>12</sup>	11	Female	Nine years	Left			
Kahn <sup>14</sup>	36	Female		Left	Three months	Without effusion	Cure
Fernet <sup>12</sup>	43	Female	Twenty-eight years	Right	Few days	Without effusion	Death*
Pastorino <sup>12</sup>	28	Male	Six years				
Dainini-Alvarez <sup>12</sup>	19	Male	Few years	Left		Without effusion	Cure
Casiello <sup>12</sup>	53	Male	Few years	Right	Four and ½ yrs.	Without effusion	Cure
Castex-Mazzei <sup>4</sup>	25	Male	Thirteen years	Left	Four and ½ yrs.	Without effusion	Cure
McGuire <sup>15</sup>	27	Female	Few years	Left		Without effusion	Cure
Faulkner-Wagner <sup>12</sup>	59	Male	Number of years	Left		Without effusion	Death
Laennec <sup>12</sup>	30	Male		Bilateral		Without effusion	Death
Harvey <sup>8</sup>	19	Male	All of life	Left	One month	Small effusion	Cure
	25	Female	Three years	Right			Cure
Bottero <sup>16</sup>	45	Male	Four years	Left		Without effusion	Cure
	88	Female	Since birth	Left		Without effusion	Cure
Casoli, Alvarez and Pedroza <sup>17</sup>	54	Male			Thirteen months	Hydropneumothorax	Death
Elliott <sup>18</sup>	44	Female	Nineteen years	Right		Without effusion	Cure
Jeffrey and Morlotte <sup>19</sup>	17	Male	One year	Left at first, then bilateral		Without effusion	Cure
Fuchs <sup>20</sup>	27	Male	One year	Right			Cure

\* Autopsy.

**Laboratory Findings.** The hemoglobin was 80 per cent, red blood cell count 4,700,000, white blood cell count 10,250, with 63 per cent polymorphonuclear leukocytes, 3 per cent eosinophiles and 34 per cent lymphocytes. The urine contained a trace of sugar and three or four white cells per high power field. The Kline and Kolmer tests were negative. No acid-fast bacilli were found in the sputum. A roentgenogram of the chest showed 50 per cent collapse of the right lung and mottling in the first interspace on the left.

**Clinical Course.** The patient was thought to have a right pneumothorax and bronchial asthma. Thoracentesis was done, and 200 c.c. of air were withdrawn from the right hemithorax. The patient's general condition grew worse and he began to have periods during which he could not be aroused. On September 16, a blowing sound was heard over the right side of the chest and was thought to indicate a possible bronchopleural fistula. Thirteen hundred cubic centimeters of air were withdrawn

from the chest on this day. The patient's condition varied. At times he was comatose and unable to respond, whereas on other occasions he was able to feed himself. Aspiration of his chest was done repeatedly. The patient died suddenly on September 18, the temperature having remained practically normal until the day before his death.

At autopsy the outstanding pathologic changes were found in the heart and lungs. The heart weighed 320 gm., and its measurements were as follows:

T. V. 13.0 cm.	P. V. 8.0 cm.	R. V. 0.2 cm.
M. V. 8.5 cm.	A. V. 7.5 cm.	L. V. 1.6 cm.

The heart was not enlarged. Its pericardial and endocardial surfaces were smooth and shiny and the right ventricular wall was somewhat thickened, and the ventricle dilated as well. The valves were thin and freely movable. The coronary vessels contained small atheromatous plaques, and one calcified area was found in the left anterior descending artery. The musculature was reddish-brown and uniformly firm. No fibrosis was grossly visible.

On microscopic examination the pericardium was found to be normal. The muscle fibers were uniform in size and staining character and there were visible pigment granules at the ends of the nuclei. There was no marked increase in fibrous tissue and the coronary vessels showed atheromatous changes.

The right lung weighed 550 gm., and the left 390 gm. The right lung was small and somewhat wrinkled on its surface, which was marked by fibrous adhesions and by occasional emphysematous blebs. At the apex some of these blebs were collapsed. The cut surface of the right lung had a mottled gray appearance and the bronchi were also prominent on this side.

The pleura was thickened by dense scar and fibrous tissue. In the majority of the sections the alveoli were partially collapsed and they contained numerous pigment-bearing macrophages. In a few areas the alveoli were widely dilated, the walls being thin and frequently ruptured. Many of them contained fibrin, lymphocytes and polymorphonuclear leukocytes. All the bronchi were dilated, the fibrous tissue around them being hypertrophied and heavily infiltrated with lymphocytes. Some of the bronchi contained large numbers of polymorphonuclear cells. There was one area in which there had been considerable hemorrhage into the alveoli.

#### PATHOLOGIC PHYSIOLOGY

As early as 1887 West<sup>1</sup> demonstrated that the normal pleura does not rupture until the intrapulmonary pressure exceeds 200 mm. of mercury. Inasmuch as such tension cannot be produced by the most severe paroxysms of coughing, rupture of the pleura presupposes some anatomic or pathologic alteration at the site of rupture.

Emphysema is a common complication of bronchial asthma. Kjaergaard,<sup>2</sup> in an extensive and thorough inquiry into the subject of spontaneous pneumothorax, was able to incriminate emphysema as the etiologic agent in only seven out of 918 cases. It is paradoxical to consider that the distention and atrophy of the lung tissue, so characteristic of emphysema, may result in extreme thinning of the alveolar wall without rupture. Studies on this problem by Zahn<sup>3</sup> have shown that, although the thickness of the alveolar wall plus that of the visceral pleura is normally 0.13 to 0.24 mm., in emphysematous lungs it may diminish to 0.05 or even 0.03 mm. Castex and Mazzei<sup>4</sup> offer, as an explanation for the rarity of rupture of the emphysematous lung, the progressive decrease in the negativity of the intrapleural pressure which occurs. Finally the intrapleural pressure be-



comes nearly positive and an equilibrium tends to be set up between the intra-pleural and intra-alveolar pressure. Thus it would appear that a protective compensatory mechanism operates to establish a steady state.

On the other hand, factors exist which may weaken the particular zone of the lung which yields. Thus, a destructive process such as tuberculosis, congenital cysts, congenital valve vesicles, emphysematous valve vesicles, and cicatricial valve vesicles<sup>5</sup> may coincide with the asthma. If the spontaneous pneumothorax is due to an erosive process resulting from the caseous destruction of lung tissue, it would be followed by pleural infection and pyopneumothorax, but this has never been shown. As Wilson<sup>5</sup> has aptly stated, the mechanism of actual rup-

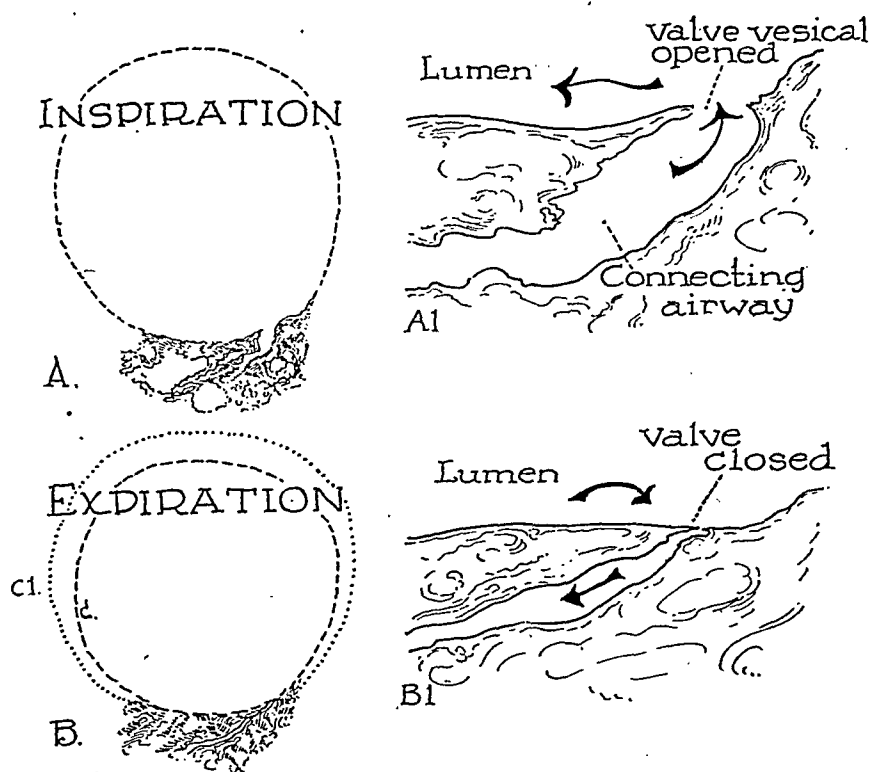


FIG. 1. Schema demonstrating the mechanism involved in the progressive increase in size of the valve vesicles.

ture is apparently the same in any of the above pathologic states. We believe that the rupture occurs through the intermediation of a valve vesicle, whatever its etiology may be. With each respiratory cycle the positive pressure increases in the valve vesicle because the nature of the lesion allows air to enter with greater ease than to leave (figure 1). In this manner a vicious cycle is initiated, so that the pleural covering of the vesicle becomes progressively thinner and, because of diminished blood supply, devitalized. Then, without any appreciable strain, the vesicle tears and a greater or lesser degree of pneumothorax results.

It has been suggested, and we believe rightly so, that the danger of rupture is greater on deep inspiration than on coughing, because then there is atmospheric pressure within the alveoli and a negative pressure without. During coughing the tendency is toward the closer approximation of the chest wall to the lung, re-

sulting in a decrease in negativity in the intrapleural space and a lessening of the positive pressure in the alveoli. Both of these factors act to preserve the integrity of the vesicle. Coughing, however, could tear the lung in marginal zones where the pressure is unequal.<sup>6</sup>

Whereas spontaneous pneumothorax can happen at any age, it usually occurs in early adult life. It is at this time that negative intrapleural pressure is greatest. In the first place the elastic recoil of the lung is greater in youth; secondly, the action of the diaphragm is more efficient in early life because, with increasing age, the central tendon becomes more fibrous, occupying a larger proportion of the total mass of the diaphragm, and, finally, the degree of emphysema is less.

Kjaergaard<sup>2</sup> and Hayoshi<sup>7</sup> have demonstrated, by means of postmortem studies on individuals dying from a variety of causes, that valve vesicles, already alluded to, actually occur. It was found that these vesicles were situated most commonly at the apices. In our case, both tear and vesicles were found in the apex.

The opinion that the most common etiologic cause of pneumothorax is tuberculosis is widely shared. Whereas tuberculosis is an etiologic factor in the causation of pneumothorax, it is the opinion of Wilson<sup>6</sup> and others,<sup>8</sup> who have had a wide experience, that tuberculosis accounts for not over 10 per cent of the cases. It may be emphasized again that no gross or microscopic evidence of active tuberculosis was demonstrated in our case. In this respect it should be pointed out that the process of healing in tuberculosis may be associated with valve vesicle formation, especially at the apices.

### DIAGNOSIS

The physical signs of pneumothorax associated with asthma do not differ from those of other etiology. The symptoms of pain, cough, dyspnea and shock are found. The first and most important physical finding is suppression of fremitus, breath and voice sounds. Hyperresonance and displacement of the heart are often demonstrable. The roentgen examination, of course, is the sine qua non of the diagnosis and without its aid many cases of minimal pneumothorax would be overlooked. This possibility should be kept in mind, particularly when the asthmatic patient complains of sudden sharp chest pain with, or without, dyspnea. The use of the tuberculin test is of great value because, when it is negative, the prognosis is extremely favorable. The main point in the differential diagnosis is the exclusion of the tubercle bacillus as the etiologic agent. Little confusion could arise in the diagnosis of traumatic pneumothorax and of that complicating pulmonary infarct, bronchiectasis, or of pulmonary abscess where the primary underlying cause should be easily recognized.

### PROGNOSIS AND TREATMENT

The prognosis in cases of pneumothorax complicating asthma is very good. As a matter of fact the condition is probably of much more frequent occurrence than has been generally appreciated. Its benignancy is attested by the fact that there are not more than three instances of postmortem studies, including our own. The nature of the underlying lesion is such that the recurrence of spontaneous pneumothorax is not common, and pulmonary tuberculosis, as a sequel, must be considered to be exceptionally rare.

Masterful neglect is the keynote of treatment because, with a minimum of therapy or none, the vast majority of these patients recover, provided the patient is not in an acute asthmatic attack. The cough may require mild sedation and, depending upon the severity of the pain, codein may be administered.

The removal of air from the pleural space has been advocated, and was practiced in the case here reported. We feel that this measure is strongly contraindicated for three reasons: (1) The equality of pressure within and without the alveolus facilitates healing of the torn vesicle; (2) removal of air and the production of a negative intrapleural pressure favor the formation of a bronchopleural fistula from which a chronic pneumothorax, or a tension pneumothorax may result; (3) the existence of a fistula favors the contamination of the pleural space. Tension pneumothorax appears to be the one indication for thoracentesis. Here action is imperative with the end in view of relieving the patient's respiratory distress rather than expanding the lung. Therefore, we advocate that these cases be treated conservatively by bed rest, for a period of two to six weeks' and with mild sedation as required.

After the site of rupture has healed, the use of air-oxygen mixtures where the concentration of oxygen approaches 100 per cent may be of real value. Fine<sup>9</sup> and his associates have advocated this based upon the experimental work of Shaw.<sup>10</sup> It will be remembered that the oxygen fraction of the air in the pleural space is rapidly absorbed, but the nitrogen fraction remains. This latter gas disappears from the tissue spaces very slowly because its diffusibility into the blood stream depends upon the small difference between its partial pressure in the tissue spaces (627 mm. of mercury) and the blood (573 mm. of mercury). Shaw<sup>10</sup> measured the fall of the partial pressure of nitrogen in the arterial blood during the inhalation of pure oxygen and found that after one hour pressure was 155 mm. of mercury, after two hours 91 mm. of mercury, after three hours 52 mm. of mercury and after four hours 31 mm. of mercury. Therefore, as Fine and his collaborators have pointed out, when pure oxygen is breathed the diffusion pressure existing between nitrogen in the tissues and that in the blood progressively increases so that one should expect a corresponding increase in the speed of absorption of nitrogen from the tissues into the blood stream whence it escapes into the expired air. Indeed, experimental evidence has been offered confirming these theoretical considerations.

If, however, the patient is having an attack of asthma, one uses the customary antispasmodic drugs, with the end in view of relieving the acute paroxysm as rapidly as possible. After the acute episode has subsided, an attempt is made to determine whether the asthma is of the intrinsic or extrinsic variety. If it is of the latter type a search is made for the offending substances, by a combination of a careful history and proper skin tests.

Materials for testing should be selected in view of the circumstances surrounding the case. For this purpose the history may be of inestimable value in directing the attention to certain possible causative agents. Further proof of this relationship is obtained by positive skin reactions to non-irritant diagnostic solutions, or at times by means of therapeutic trial.

The specific method of treatment is dependent on the etiologic factors unearthed by the diagnostic survey. It may be summed up, then, by saying that therapy consists in the elimination of the offending agents whenever this may be

done. When this is not feasible for one reason or another, specific or non-specific desensitization is inaugurated. Numerous forms of non-specific therapy are also employed.

### SUMMARY

A fatal case of spontaneous pneumothorax in an asthmatic patient has been described. An attempt has been made to explain the mechanism involved, and on the basis of this, the etiology, physiology, symptomatology, diagnosis and treatment are discussed.

### BIBLIOGRAPHY

1. WEST, S.: The Bradshawe Lecture on Pneumothorax, *Brit. Med. Jr.*, 1887, ii, 393.
2. KJÆGAARD, H.: (a) Spontaneous pneumothorax in the apparently healthy, *Acta. med. Scandinav.*, 1932, xliii (Supp.), 1. (b) Pneumothorax simplex, *Ibid.*, 1933, lxxxiii, 93.
3. ZAHN, F. W.: Ueber die Entstehungsweise von Pneumothorax durch Continuitätstrennung der Lungenpleura ohne eitrige Entzündung, *Virchow's Arch. f. path. Anat.*, 1891, cxxiii, 197.
4. CASTEX, M. R., and MAZZEI, E. S.: Pneumothorax spontané dans l'asthme, *Presse Méd.*, 1938, xlii, 529.
5. WILSON, J. L.: Spontaneous pneumothorax, *Internat. Clin.*, 1937, i, 157.
6. WILSON, J. L.: Personal communication.
7. HAYOSHI, J.: Cited by KJÆGAARD.<sup>2</sup>
8. HARVEY, C.: Asthma complicated by spontaneous pneumothorax, *Med. Jr. Australia*, 1938, ii, 950.
9. FINE, J., HERMANSON, L., and FREHLING, S.: Further clinical experience with 95 per cent oxygen for the absorption of air from the body tissues, *Ann. Surg.*, 1938, cvii, 1.
10. SHAW: Cited by FINE.<sup>9</sup>
11. DERBES, V.: Asthma then and now, *New Orleans Med. and Surg. Jr.*, 1942, xciv, 582.
12. LAENNEC, R. T. H.: Cited by CASTEX and MAZZEI.<sup>4</sup>
13. SPIVAK, C. A.: Asthma with pneumothorax, *Med. Jr. and Rec.*, 1925, cxxii, 10.
14. KAHN, I. S.: Spontaneous pneumothorax due to bronchial asthma, *Texas State Jr. Med.*, 1933, xxv, 781.
15. MCGUIRE, H. H.: A case of pneumothorax occurring in bronchial asthma, *Virginia Med. Monthly*, 1924, li, 167.
16. BOTTERO, A.: Il pneumotorace spontaneo negli asmatici, *Athena*, 1939, viii, 372.
17. CASOLI, C. A., ALVAREZ, V., and PEDROZA, R. O.: Neumotorax espontaneo en el asma, *Rev. de cien. méd.*, 1938, i, 90.
18. ELLIOTT, R. W.: Subcutaneous emphysema and pneumothorax in bronchial asthma, *Lancet*, 1938, i, 1104.
19. JEFFREY, G. S., and MORLOTTE, D. C.: Simultaneous bilateral spontaneous pneumothorax complicating bronchial asthma, *Canad. Med. Assoc. Jr.*, 1938, xxxix, 171.
20. FUCHS, S. M.: Spontaneous pneumothorax in an asthmatic patient treated with iodized oil, *New York State Jr. Med.*, 1937, xxxix, 791.

## EDITORIAL

### *SALICYLATES IN THE TREATMENT OF RHEUMATIC FEVER*

ALTHOUGH salicylates have been used in the treatment of rheumatic fever for nearly seventy years, there is still a wide divergence of opinion as to the degree of their effectiveness. There is no doubt as to their ability, even in moderate doses (up to six grams a day), to relieve the pains of arthritis, to alleviate the local manifestations of inflammation in the joints and usually to control the fever, at least temporarily. There is also general agreement that they do not exert a direct destructive action on the infectious agent. There is more difference of opinion as to their influence on the vascular and cardiac lesions. Thus far, however, there has been no convincing proof that salicylates significantly reduce the incidence of such lesions. This is a crucial point in treatment, since the disability and mortality in rheumatic fever are so largely a result of vascular and cardiac injury.

This uncertainty is due in part to ignorance of the mode of action of salicylates, and to rather haphazard methods of administration, as well as to the previous lack of means of precisely controlling their administration. Another difficulty has been the lack of knowledge of the etiology and pathogenesis of the disease itself.

Although no infectious agent has yet been demonstrated in rheumatic fever, there is considerable indirect evidence that hemolytic streptococci are in some way involved. It is well known that an acute streptococcal pharyngitis often precedes an acute attack of rheumatic fever by one to three weeks. Also a marked increase in titer of circulating antibodies, particularly of antistreptolysins, accompanies an acute attack. No living agent has been demonstrated in the joints or tissues of the cardiovascular system, however, and if a streptococcus is really the etiological agent, its action must be exerted in some indirect way.

Many investigators have suggested that the local lesions in the tissues in rheumatic fever are manifestations of an allergic or anaphylactic reaction. Attempts to reproduce the lesions by injections of bacteria into sensitized animals have not led to convincing results. Recently, however, Rich and Gregory<sup>1</sup> have reported the production of lesions showing the fundamental characteristics of those of rheumatic fever by producing serum disease in animals. They<sup>2</sup> have also pointed out the close resemblance of the pulmonary lesions in rheumatic fever to those in cases of hypersensitiveness to sulfonamides.

<sup>1</sup> RICH, A. R., and GREGORY, J. E.: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity, *Bull. Johns Hopkins Hosp.*, 1943, lxxiii, 239-264.

<sup>2</sup> RICH, A. R., and GREGORY, J. E.: On the anaphylactic nature of rheumatic pneumonitis, *Bull. Johns Hopkins Hosp.*, 1943, lxxiii, 465-478.

Coburn and Pauli<sup>3</sup> have furnished indirect evidence of another type in support of this view. They showed that a positive precipitin reaction occurs when serum obtained during the acute phase of rheumatic fever is mixed with serum obtained during the symptomless period of about two weeks ('phase 2') that intervenes between the initial pharyngitis and the acute outbreak. They interpret this as indicating that during the symptomless period (which might be regarded as the incubation period) the serum contains precipitinogen, presumably produced by the streptococci in the pharynx. At the onset of the acute phase, antibody (precipitin, antistreptolysin) appears in quantity in the plasma, and they have found an approximate correlation between the antibody titer and the severity of the attack. The tissue inflammation they regard as the result of a reaction, anaphylactic in type, between this antibody and the circulating antigen.

The action of salicylates in alleviating the inflammation and the symptoms associated with it must be accomplished, they think, by interfering in some way with this reaction. Coburn and Kapp<sup>4</sup> carried out some in vitro experiments to test this hypothesis. They found that salicylates did diminish the amount of precipitate formed when horse serum euglobulin or egg albumin was mixed with the corresponding antiserum. This inhibition appeared to be due to interference with the antibody. A relatively high concentration of salicylate was required, however, and its inhibitory action was diminished if an excess of antibody was present.

These observations suggested that if salicylates act in the same way in vivo, their effectiveness in rheumatic fever would depend upon securing a sufficient concentration in the blood, i.e., upon adequately high dosage. Furthermore, if this could be accomplished promptly in the initial attack, one might hope that the development of the damaging vascular and cardiac lesions could be forestalled.

Based on such premises, Coburn<sup>5</sup> has carefully studied (over a two year period) a series of cases of rheumatic fever treated with varying doses of salicylates. He attempted to gauge the activity of the infection in the absence of clinical symptoms by means of the sedimentation rate. He also devised a relatively simple method of measuring the amount of salicylate in the blood plasma as an additional control of the dosage.

In one group of 63 cases who were treated with small doses of salicylates (three to six grams a day), symptoms were relieved, but there was not a progressive fall in the sedimentation rate. These cases showed a plasma salicylate content below 250 gamma per c.c. About 40 per cent of these cases had recurrent attacks, and 21 cases developed signs of valvular disease.

<sup>3</sup> COBURN, A. F., and PAULI, R. H.: A precipitinogen in the serum prior to the onset of acute rheumatism, *Jr. Exper. Med.*, 1939, lxi, 143-162.

<sup>4</sup> COBURN, A. F., and KAPP, E. M.: The effect of salicylates on the precipitation of antigen with antibody, *Jr. Exper. Med.*, 1943, lxxvii, 173-184.

<sup>5</sup> COBURN, A. F.: Salicylate therapy in rheumatic fever. A rational technique, *Bull. Johns Hopkins Hosp.*, 1943, lxxiii, 435-464.

In another group of cases, 10 grams of salicylate per day were administered. Those who received the drug by mouth usually became free from symptoms within 24 to 48 hours and afebrile within 72 hours. The plasma salicylate level after 24 to 48 hours ranged from about 350 to 400 gamma per c.c. If 10 grams per day were administered by intravenous infusion, these levels were reached immediately, and symptoms and fever usually subsided within 24 hours. Two cases not showing satisfactory improvement, who were given 20 grams by infusion during the second day, then showed a prompt response with a plasma salicylate level of 600 gamma per c.c. The improvement could usually be maintained by daily administration of 10 grams by mouth. The sedimentation rate in these cases fell progressively to normal within 14 days. Treatment at this level was routinely continued for two weeks longer, and was then interrupted. Two cases showed a recrudescence which was promptly controlled by resumption of treatment. None of the 38 cases receiving 10 grams of salicylate per day developed signs of valvular disease during the period of observation, although a number showed electrocardiographic abnormalities at the onset of treatment.

According to Coburn, the only toxic symptom ordinarily observed, even with maximal doses, was a "mild tinnitus." One case, however, after 10 days' satisfactory treatment abruptly developed alarming symptoms of intoxication (fever, psychosis, cutaneous eruption), and the drug had to be permanently stopped. These symptoms subsided within three days, but two days later there was a severe recrudescence of rheumatic fever with a rapid rise in the sedimentation rate.

On the basis of these observations Coburn has proposed a method for administering salicylate effectively, for the details of which the reader is referred to his article. He stresses the importance of early treatment, of securing promptly an effective concentration of salicylate in the plasma and maintaining this until the activity of the infection has subsided, using intravenous infusions if necessary, and of controlling treatment by determinations of the sedimentation rate rather than by the clinical symptoms. He emphasizes the point that smaller doses may relieve symptoms while masking a progressive inflammatory process in the tissues.

If Coburn's observations and conclusions are correct, their great importance is obvious. Many clinicians in the past have advocated the use of large doses of salicylates (10 to 12 grams a day) in rheumatic fever. Few, however, have probably appreciated the need of continuing these doses for such a protracted period after all clinical manifestations of illness have subsided. From the standpoint of practical therapeutics this point together with more adequate methods of controlling treatment constitute Coburn's major contribution. Those who have had experience with the administration of large doses of salicylate may well doubt whether the incidence of toxic symptoms will continue to be as low in a larger series of cases. Coburn's work manifestly requires confirmation in other clinics where treatment can be

adequately controlled and critically judged. A much more protracted period of observation is also necessary for its evaluation. In view of the importance of the subject, such studies will undoubtedly be forthcoming. The practical value of this therapeutic procedure is obviously independent of the validity of the hypothesis as to the mechanism by which the effect of salicylate is brought about.

Coburn recognizes the fundamental defect of salicylate, that it does not destroy the infectious agent of rheumatic fever. Until some means of doing this is discovered, however, any measure which will limit the devastation that it causes will be valuable.



## REVIEWS

*Technic of Electrotherapy and Its Physical and Physiological Basis.* By S. L. OSBORNE, Assistant Professor, Department of Physical Therapy, Northwestern Medical School, and H. J. HOLMQUEST, Lecturer in Applied Physics at the same institution, Research Engineer for General Electric X-ray Corporation. 780 pages;  $23.5 \times 15$  cm. 1944. Charles C. Thomas, Springfield, Illinois. Price, \$7.50.

The material of this book, the most noteworthy peak of electrotherapeutic bibliography in a decade, based on the authors' 16 years experience in teaching physicians, technicians, and medical students at Northwestern, falls in four categories: (1) Direct current; (2) Electrical muscle stimulation; (3) Radiation, thermogenic, and U.V.R.; (4) High frequency, (a) conventional, (b) shortwave, (c) surgical, (d) fever therapy. Each has its respective chart of indications and technic.

As a self instruction guide to the why as well as how and what of electrotherapy to those with a good grounding in science and to those whose scientific training is limited, an accompanying handbook of graded electrophysics or an ample glossary of terms, such as radan, ketone, farad, dynes, Debye units, microerg, etc., would be extremely helpful. Nomenclature of electrotherapy is clarified. Emphasis is given to rulings of the Council on Physical Therapy.

The Direct Current chapter opens with rules for a written prescription, a feature emphasized throughout. These have, within limits, an elasticity for which a technician is grateful.

There is a thorough discussion of ionizations with a table of substances used with polarity for each indicated. Copper ionization for fungus infections to hands and feet is given in detail. From the table in the Handbook of Physics and Chemistry, the electrochemical equivalents of metals most frequently employed in ion transfer are given, and in this instance, the milligrams of copper liberated are worked out:

30 minutes = .5 hour

15 minutes = .015 ampere

0.5 hour  $\times$  .015 ampere = .0075 amperes hours

$.0075 \times 1.119$  (electrochemical grams per ampere hour) = .008925 or 8.9 milligrams

The chapter on muscle stimulation reviews the recent physiology and applies the necessary procedures. The summary is quoted in full:

"The types of current fully adequate and most desirable in clinical practice for the electrical stimulation of muscle are in our opinion:

"A. The surging interrupted D.C. with Alternate Polarity, having a surge frequency of 5-100 per minute and being interrupted from 40-100 times per second (ratio periods of surge to rest are further described as being 2-1).

"B. The surging uninterrupted D.C. with Alternate Polarity having a surge frequency of 5-20 per minute."

Two chapters follow covering apparatus, early and recent, and technics.

Radiation starts with definitions of wave lengths and their respective placements in the spectrum. "The entire known electromagnetic spectrum extends from 30,000 meters to less than .01 angstrom unit in wave length—a range covering 60 octaves, only one of which, namely from 4,000—8,000 angstrom units, excites the sensation of vision. If a scale one foot long were to represent the visible spectrum, a linear scale

approximately 15 million miles long would be required to represent the 60 octaves of known radiation. Life on this planet evolved and developed in this complex radiation environment. Modification of it has marked biologic effects on both plants and animals. Radiation properly used provides a potent therapeutic and disease preventing agency. The radiations with which this discussion is primarily concerned are the infrared and the U.V.R. lying respectively in the spectral ranges 8,000-150,000 A.U. and 2,000 to 3,000 A.U."

The physics of refraction are discussed with mathematical detail.

Defining thermogenic radiation as heat producing radiation, it includes and replaces the terms phototherapy, radiant heat therapy, infrared therapy, and, to quote, "the vague misnomer deep therapy." Bodily effects are subdivided with appropriate discussions.

Ultra violet radiation is ably discussed. The chapter on artificial sources, hot body radiators, electric arcs, and glow discharges, concludes with a caption from the Council of Physical Therapy. "The fact that the erethemogenic efficiency of a source is high is not necessarily a criterion of its suitability for therapeutic purposes." For information on specific apparatus, the student is referred to the booklet *Apparatus Accepted* by the Council on Physical Therapy.

Four hundred and twenty-nine pages, over half the book, deal with high frequency currents. Over half of these pages cover the technic of local applications and fever therapy. This is perhaps a criterion of its importance to the authors.

Before considering alternating currents of high frequency, there is a brief study of alternating current circuit theory in general. Modifications of Ohm's Law as applied from D.C. currents to alternating currents, through different types of basic circuit elements, such as condensers, coils, and pure resistance, also the influence on the opposition these basic circuit elements oppose to the flow of A.C. This brings one to a consideration of inductance, inductance reactance, capacitance, admittance, susceptance resonance, current lags, with exact definitions, applied electrical laws, and problems with definite mathematical formulae.

The above principles are applied to the alternating currents of conventional diathermy and later to the diode and triode thermionic tubes with their electric and magnetic fields. Criticism is made of the term short wave diathermy. "It was undoubtedly suggested by the fact that relatively short radio waves are radiated into space from the high frequency current flowing in the currents of an oscillator. The term is somewhat misleading since it suggests that a patient is treated by a radiation field, whereas the fact is that the patient is definitely made part of a high frequency circuit, coupled relatively closely to the tank circuit of an oscillator."

The induction method of application is favored in technic of application. Briefly, the reasons given on p. 485 are:

1. The induction field generates heat in an electrolyte in direct proportion to its conductivity. Heat is dominantly produced thereby in the vascular type of tissue.
2. It is in the vascular tissues that the body normally produces heat.
3. It is through the agency of the blood stream that the living body combats infection, relieves congestion, brings about elimination and repair.
4. Induction currents applied to vascular tissue best aid the body to do its work.
5. The use of the induction field is indicated in all conditions benefited by the production of an active hyperemia.

On p. 490, No. 8, the use of high frequencies of any sort to patients in metal beds is frowned upon, "Should the use be unavoidable, special precautions should be taken." Out of 40 pictures dealing with the application of induction currents, 15 are evidently in modern metal hospital beds, and there is no mention of precautions hav-

ing been taken. This occurrence in such an important book is one of the small things prolonging confusion of thought and technic about treatment.

Greater adaptability of treatment to pathology is recommended. "For certain pathologies, short treatments given at intervals throughout the day may be indicated, while for other pathologies, long periods of low intensity treatment may be more effective." Speaking of orificial electrodes, the authors express themselves in italics: "*In our opinion, generalized pelvic heating is just as effective and probably preferable for the treatment of vaginal, rectal, and prostatic conditions.*" It is pointed out that condenser pad applicators are unacceptable to the Council on Physical Therapy as they are incapable of permitting a final temperature of 103°–104° F. in the deep muscles of the thigh at the end of a twenty minute application. Cuffs are acceptable to the Council for extremities only. Electrosurgery is simplified by numerous references to the book by Kelly and Ward, Saunders Company, Philadelphia—London, 1932.

Modern experimentation is discussed at length with direction implied to future investigations. The more than hundred pages on fever therapy cover at length bodily effects with emphasis on effects on blood.

From its suggested definite but elastic prescriptions, to its backbone of scientific rationale, this is the most thought provoking book on electrotherapy that has yet appeared, an adequate reflection undoubtedly to the valuable research being done at Northwestern.

G. E. S.

*A Manual of Physical Therapy.* Third Edition, Thoroughly Revised. By RICHARD Kovács, M.D., Professor of Physical Therapy, New York Polyclinic Medical School. 309 pages; 20.5 × 14 cm. 1944. Lea and Febiger, Philadelphia. Price, \$3.25.

In his preface the author states, "a concise manual on physical therapy should serve as a welcome aid in elementary courses on this subject as well as for physicians and medical personnel seeking information on essential facts." The book fulfills the author's design aptly.

The packing of much information in small compass is illustrated by the following paragraph, one of three, on physiological effects of hyperthermy: "The pulse-rate increases in proportion to from 5–9 beats per minute to each degree Fahrenheit. The respiration also increases at a rate of about 2–12 per minute to an increase of 1° F. At a temperature of about 105° F. it is about 25 to 30 per minute. The blood pressure at first undergoes a slight elevation of systolic pressure, then declines. The diastolic pressure falls, as a rule, as soon as the temperature begins to rise, and its usual range is from 60–50 mm. in contrast to 120–80 mm. for the systolic. The basal metabolic rate increases at a rate of about 7% for each degree rise in temperature. Every person, who has undergone five hours or more of fever therapy, will lose from four to five pounds of weight due to the fluid excreted by perspiration. The kidney secretion is increased at first—later there is evidence of concentration of urine. The loss of chlorides through perspiration may amount to 2.6 grams in one febrile session. All these changes return to normal after a few hours."

The physics of thermionic and amplifier tubes are diagrammed clearly, rivalling the text. The chapter on galvanism ends with exactly noted polarity use in technics of iontophoresis for each drug named. The newer machines, combining motor wave mechanism with rectifying tube is shown (Courtesy MacIntosh Company). "Thermionic types of low frequency generators have come into use in recent years. They utilize vacuum tubes for rectifying the alternating currents and 'grid glow' tubes to rhythmically change its strength without any sort of rotating mechanism; other

thermionic devices serve to interrupt its flow." The advantage of these generators is their lower cost and absence of moving parts, with silent operation and no need of lubrication (figure 59, Courtesy Wappler, Inc.).

The basic physics of vacuum tube apparatus is an agreeably plain first lesson. The Hemingway chart of an oscillator tube mechanism is on page 153 (Courtesy Archives of Physical Therapy), and the tube itself on page 154 (Courtesy Westinghouse).

A chapter on baths illustrates full galvanic and partial galvanic and ends with a discussion on hypothermy, in both anesthetic and peripheral vascular conditions. The commending baton of the author falls heavily on the latter.

Dr. Madge C. L. McGuinness contributes a valuably suggestive chapter on exercise. She stresses the three R's—Rest, Relaxation, and Recreation, never more necessary nationally than today. Exercises for spastics and hemiplegias, in our opinion, should be based entirely on the stretch reflex concept so ably developed in exercises for this group by Dr. Phelps. If that concept is not at the base of exercise plans, exercise for this group too often does harm to body and personality.

The author concludes with a chapter on physical therapy in institutional practice. Training, departmental plans, and records share emphasis.

There is no bibliography. References are scattered through the text.

To start any beginner on the right road, the book is painstakingly clear.

G. E. S.

*Physical Medicine in General Practice.* By WILLIAM BIERMAN, M.D., Mount Sinai Hospital and N.Y.U. Medical College, N.Y. 654 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, \$7.50.

This is a general easily readable guide to physical medicine. Stress goes on pathologies, which take a full third of the book, and clinical measures of their treatment.

Climatotherapy and Spa Therapy form a chapter discussion early in the book. Numerous American spas are individualized by name and quality. The chapter and its ample index should stimulate development of the home field, as it were, in this too little developed therapy.

The author reviews some of his experiments in visible and infrared therapy. He finds the near infrared decidedly more effective in raising subcutaneous temperature than those lamps mainly infrared. The heating source in the experiments was a 260 watt carbon filament lamp held 18 inches from skin surface. Preferred dosage is optimum, not maximum. Obviously the optimum varies with varying factors in individual cases.

The conventional form of diathermy with the making of usual and unusual electrodes as vaginal electrodes from human plaster casts, and facial masks of plaster, lined with tinfoil, for the individual face, form the newer part of that topic. A warning not to discard the simple forms of heat with conventional diathermy for short wave diathermy indicates that, to this author, each has its own place. Short wave diathermy is spoken of as short wave therapy. A lucid easily understandable exposition is followed by specific technics, dosage determination, duration, frequency, preparation of patient, and precautionary measures with contraindications.

The history of fever therapy is outlined. Apparatus is discussed in detail. The author emphasizes the careful choice of the fever therapy technician. "A good technician, even though she works with relatively poor apparatus, is far better than a poor technician with the best type of apparatus." He emphasizes adequate and exact preparation of the patient for the day before and for the therapy day itself. Morphine and seconal are sedatives of choice, preferably combined. "It should be

borne in mind that morphine and the barbiturates may so disturb the control of the heat centers that a further rise in body temperature follows their administration. At 101° or 102° this may not be important but it obviously becomes a matter of vital importance if this sudden elevation occurs when the patient's temperature has reached 106° or 106.5°. The temperature should first be lowered a degree or two." Later, when intravenous administration seems desirable, we give 1000 c.c. of physiologic salt containing 5% sugar. Again, in the more serious type of cyanosis, it may be necessary to terminate the treatment abruptly; to reduce the temperature of the body as quickly as possible, and to give carbon dioxide and oxygen inhalations with salt solution intravenously. Undoubtedly due to these and other careful precautions similarly outlined, the author can state, "In my own experience, embracing several thousand treatments, there has been but one death."

The pathological changes leading to death during fever therapy form an exact and interesting discussion.

Indications for electrosurgery with its disadvantages are tabled on pages 214 and 215.

Iontophoresis rates a full discussion as does galvanic technic. Electrolysis is given in full. Electrodiagnosis amplified with splendidly drawn charts (not signed), chronaxies, and their significance, are discussed. "The Schnee bath is sometimes used to induce movement of the muscles of the extremities en masse." "Spas abroad use the general galvanic treatment in full length tubs at 95° with electrodes out of the patient's reach, and the tub grounded." Indications and contraindications are fully outlined.

Metabolic changes form an important section of the chapter on ultra-violet radiation with the notation that while overdosage of Vitamin D may result from excess oral medication it does not occur from an overexposure to photochemical radiation, also that "radiation is ineffective in the presence of dietary deficiency of calcium and phosphorus." Ultra violet radiation of the blood in cases of peritonitis, puerperal sepsis, post-abortion sepsis, bacteremia or toxemia is recommended as a safe procedure following the technic developed by E. K. Knott of Seattle. The blood is drawn from a vein in the arm, citrated, drawn from the container by a pump and intensely irradiated by a water-cooled quartz mercury lamp. The author's more simple technic follows: "the removal of about 5-8 c.c. of blood which is citrated, irradiated with a mercury vapor lamp and then injected intramuscularly. Injections are repeated two or three times a week for from fourteen or eighteen times. This method is proposed for the relief of pain in arthritis and in chronic muscular rheumatism, or in the treatment of acute allergic diseases of the skin. This is really a form of protein therapy."

Massage, exercise and occupational therapy detailed, fill out the physical medicine scheme.

The sketches on exercise surprise one. They do not follow in all instances good exercise technic. Figures 191 and 205 are notable offenders. Foot extensors in the series seem needlessly put to a strain, while exercise of another part is being performed. This is a regrettable occurrence in a new book by an outstanding author.

Conduct of Treatments forms a short valuable chapter. Written prescriptions are desirable. Hibben says, "that when a department is in charge of a physician trained in physical medicine and when his assistants are registered P.T. technicians, the medico legal liability of the hospital is diminished about 90%." This point has connotations to medical students in doubt about a specialty. The paragraphs on departmental accidents rate study, not only by technicians and physicians, but by hospital administrators, as does the appendix giving required hospital specifications of apparatus for the City of New York. Council approval is obvious but not stated.

G. E. S.

## BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Simplified Diabetic Management.* 4th Edition. By J. T. BEARDWOOD, JR., A.B., M.D., F.A.C.P., and H. T. KELLY, M.D., A.A.C.P. 172 pages; 19.5 × 13.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, \$1.50.

*Leukopenia and Agranulocytosis.* By WILLIAM DAMESHEK, M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). (Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work.) 78 pages; 24 × 16 cm. 1944. Oxford University Press; New York City. Price, \$1.75.

*The Gastro-Intestinal Tract. A Handbook of Roentgen Diagnosis.* By FRED JENNER HODGES, B.S., M.D. 320 pages; 21 × 14.5 cm. 1944. Year Book Publishers, Inc., Chicago. Price, \$5.50.

*Surgical Disorders of the Chest. Diagnosis and Treatment.* By J. K. DONALDSON, M.D., F.A.C.S. 364 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia. Price, \$6.50.

*The Practice of Medicine.* Fourth Edition. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D. 1444 pages; 26 × 18 cm. 1944. C. V. Mosby Company, St. Louis. Price, \$10.00.

*Fundamentals of Internal Medicine.* Second Edition. By WALLACE MASON YATER, A.B., M.D., M.S. in (Med.), F.A.C.P. 1204 pages; 25 × 17.5 cm. 1944. D. Appleton-Century Co., New York City. Price, \$10.00.

*The Art of Anaesthesia.* Seventh Edition. By PALUEL J. FLAGG, M.D. 519 pages; 23.5 × 16.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, \$6.00.

*X-Ray Examination of the Stomach.* By FREDERIC E. TEMPLETON, M.D. 516 pages; 23.5 × 16 cm. 1944. University of Chicago Press, Chicago. Price, \$10.00.

*Manual of Psychological Medicine.* By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S.E. 298 pages; 22 × 14.5 cm. 1944. Williams & Wilkins Company, Baltimore. Price, \$5.00.

*A New German-English Psycho-Analytical Vocabulary.* By ALIX STRACHEY. 84 pages; 22 × 14.5 cm. 1943. Williams & Wilkins Company, Baltimore. Price, \$2.50. (Research Supplements to the International Journal of Psycho-Analysis. Edited by Edward Glover. No. 1.)

*Keys to the Mosquitoes of the Australasian Region, Including a Synopsis of Their Distribution and Breeding Habits.* By KENNETH L. KNIGHT, Lieut., H-V(S), USNR, RICHARD M. BOHART, Lieut.(jg), H-V(S), USNR, and GEORGE E. BOHART, Lieut., H-V(S), USNR—U. S. Naval Medical Research Unit No. 2. 71 pages; 28 × 22 cm. 1944. National Research Council—Division of Medical Sciences. Issued by the Office of Medical Information (under grant of Johnson & Johnson Research Foundation).

*Antimalarial Drugs. General Outline.* By OWSEI TEMKIN, M.D., and ELIZABETH M. RAMSEY, M.D. 128 pages; 28 × 22 cm. 1944. National Research Council

—Division of Medical Sciences. Issued by the Office of Medical Information (under grants of the Carnegie Corporation and the Johnson & Johnson Research Foundation).

*Spontaneous Pneumothorax.* By JAMES J. WARING, M.D. 34 pages; 28 × 22 cm. 1944. National Research Council—Division of Medical Sciences. Issued by the Office of Medical Information (under grant of the Johnson & Johnson Research Foundation).

*The Blood Plasma Program.* By JAMES A. PHALEN, M.D., Colonel, U. S. Army. 67 pages; 28 × 22 cm. 1944. National Research Council—Division of Medical Sciences. Issued by the Office of Medical Information (under grants of the Carnegie Corporation and the Johnson & Johnson Research Foundation).

## COLLEGE NEWS NOTES

### A. C. P. MEMBERS IN THE ARMED FORCES

Dr. John S. Staneslow, F.A.C.P., Waterbury, Conn., recently entered the armed forces of the United States. 1,715 Fellows or Associates of the College have been commissioned during the present war; many others have volunteered but were not accepted for various reasons.

Several members have been honorably discharged from active duty, including the following:

Lt. Col. Dwight Lawson, (MC), USA—June 30, 1944  
Brigadier Jonathan C. Meakins, RCAMC—September 7, 1944  
Captain E. David Sherman, RCAMC—June 10, 1944  
Lt. Comdr. Warren F. Kahle, (MC), USNR—July 1, 1944  
Captain Elmer E. Kottke, (MC), AUS

---

### NEW LIFE MEMBER

Dr. Harold S. Davidson, F.A.C.P., Atlantic City, N. J., became a Life Member of the College on September 13, 1944.

---

### GIFTS TO THE COLLEGE LIBRARY

The following gifts are gratefully acknowledged:

#### *Books*

Dr. Harry L. Arnold, Sr., F.A.C.P., Honolulu, T. H.—“Poisonous Plants of Hawaii.”  
Dr. T. Lyle Hazlett, F.A.C.P., East Pittsburgh, Pa.—“Introduction to Industrial Medicine.”

#### *Reprints*

Dr. John J. Andujar, F.A.C.P., Fort Worth, Tex.—1 reprint.  
Dr. George E. Baker, F.A.C.P., Casper, Wyo.—4 reprints.  
Joseph L. Holland, (Associate) Captain, (MC), AUS—1 reprint.  
A. M. Hutter, F.A.C.P., Lieutenant Commander, (MC), USNR—1 reprint.  
Morrill L. Iisley, F.A.C.P., Claremont, Calif.—1 reprint.  
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—1 reprint.  
Dr. Samuel G. Shepherd, F.A.C.P., Philadelphia, Pa.—2 reprints.  
Paul S. Strong (Associate), Captain, (MC), AUS—1 reprint.  
Dr. Howard Wakefield, F.A.C.P., Chicago, Ill.—1 reprint.  
Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—2 reprints.

---

### A.C.P. BOARD OF REGENTS WILL MEET DECEMBER 16

The regular autumn meeting of the Board of Regents of the College will be held at the College Headquarters in Philadelphia, December 16, 1944. On the preceding day, December 15, there will be held in Philadelphia a Regional Meeting of the College for Eastern Pennsylvania, New Jersey and Delaware. Also, the various Committees of the College will meet and prepare their reports, December 15.



## DEADLINE FOR PROPOSAL OF CANDIDATES

Proposals of candidates for Associateship or Fellowship for review by the Committee on Credentials on December 15, and final action by the Board of Regents on December 16, must be filed with the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa., at least thirty days in advance thereof, or by November 15, 1944.

## VANCOUVER REGIONAL MEETING OF THE COLLEGE

A Regional Meeting of the American College of Physicians and a War-Time Graduate Medical Meeting was held at the Hotel Vancouver, Vancouver, B. C., September 14-15, for the territory embracing Idaho, Oregon, Washington, Alberta, British Columbia, Manitoba and Saskatchewan. Dr. George F. Strong, Regent of the College, of Vancouver, was the General Chairman and the Governors of the participating States and Provinces constituted the Executive Committee.

The program was as follows:

THURSDAY, SEPTEMBER 14

*Morning Session*

*Presiding*

T. HOMER COFFEN, F.A.C.P.

*Regent, Portland, Oregon*

"The Recent Status of Rickettsia Disease." Dr. Matthew Riddle, Associate Professor of Medicine, University of Oregon Medical School.

"Control of Staphylococcic Infections with Sulfonamide Drugs." Lieut. Col. Roy H. Turner, Chief of the Communicable Disease Treatment Branch, Army Service Forces, Washington, D. C.

"Clinical Experience with Penicillin." Capt. Chas. E. Watts, F.A.C.P., Medical Officer in Command, United States Naval Hospital, Seattle, Wash.

"Some Pharmacological Problems in the Use of Chemotherapeutic Drugs." Dr. Norman D. Davis, Professor of Pharmacology, University of Oregon Medical School.

*Luncheon*

*Presiding*

J. W. SCOTT, F.A.C.P.

*Governor, Edmonton, Alberta*

*Speaker*

MAJ. GEN. G. R. PEARKES, V.C., C.B., D.S.O., M.C. G.O.C. in C. Pacific Command

*Afternoon Session*

*Presiding*

E. G. BANNICK, F.A.C.P.

*Governor, Seattle, Washington*

"Respiratory Limitations in Altitude Flying." Group Capt. G. E. Hall, Consultant in Medicine, R.C.A.F., Ottawa, Ontario.

"Respiratory Disease Problems in an East Coast Base." Surgeon-Comdr. J. Wendell MacLeod, Consultant in Medicine, R.C.N.V.R., Halifax, N.S.

"Visualization of the Chambers of the Heart and Great Vessels." Lieut. Comdr. Israel Steinberg, M.C.-V's, U.S.N.R., F.A.C.P.

"Experimental and Clinical Aspects of Carotid Sinus Reflexes." Dr. Hance Haney, Professor of Physiology, University of Oregon Medical School.

*Dinner*

7:00 P.M.

*Presiding*

G. F. STRONG, F.A.C.P.

*Regent*, Vancouver, B. C.

*Speakers*

DAVID P. BARR, F.A.C.P.

President-elect American College of Physicians  
New York City

COMMANDER CORYDON M. WASSELL (M.C.)  
U.S.N.R.

FRIDAY, SEPTEMBER 15

*Morning Session*

*Presiding*

G. M. POINDEXTER, F.A.C.P.

*Governor*, Boise, Idaho

"Hepatitis." Lieut. Col. Roy H. Turner, Chief of the Communicable Disease Treatment Branch, Army Service Forces, Washington, D. C.

"Psychosomatic Medicine." Brig. W. P. Warner, Deputy Director General of Medical Services, Ottawa, Ontario.

"Gastroenterological Problems in the Canadian Navy." Surgeon-Comdr. J. Wendell MacLeod, Consultant in Medicine, R.C.N.V.R., Halifax, N.S.

"Some Principles and Problems in Immunity." Dr. C. E. Dolman, Head of Department of Bacteriology and Preventive Medicine, University of British Columbia, and Director of Provincial Laboratories.

"Thiouracil in Graves' Disease." Dr. David P. Barr, F.A.C.P., Professor of Medicine, Cornell University Medical College, New York City.

*Afternoon Session*

*Presiding*

HOMER P. RUSH, F.A.C.P.

*Governor*, Portland, Oregon

"Body Section Radiography." Comdr. Wendell G. Scott, M.C.-V's U.S.N.R.

"Maintenance of Normal Body Temperature in Service Personnel." Group Capt. G. E. Hall, Consultant in Medicine, R.C.A.F., Ottawa.

"Some Experience with the Use of Gold Salts in the Treatment of Arthritis." Dr. P. H. Sprague, F.A.C.P., Assistant Professor of Clinical Medicine, University of Alberta.

"Observations on Active Rheumatic States." Dr. John MacEachern, F.A.C.P., Assistant Professor of Medicine, University of Manitoba.

"Malaria Control"—with two films. Lt. Commander Frank P. Mathews, Malaria Indoctrination Officer, 13th Naval District, Seattle, Wash.

---

#### AMERICAN COLLEGE OF SURGEONS CANCELS 1944 CLINICAL CONGRESS

By action of its Board of Regents, the American College of Surgeons has cancelled its Annual Clinical Congress for 1944 because of the acute war situation, involving greater demands than at any time in the past upon our transportation for the carrying of wounded military personnel, troops and war materiel. The Congress was to have been held in Chicago, October 24-27.

---

#### AID TO LIBRARIES IN WAR AREAS

Up to the end of 1943, \$160,873.62 has been spent for subscriptions to 325 scholarly and scientific journals, to be stored in this country, for distribution after the war to libraries in war areas. Funds were provided by grant by the Rockefeller Foundation, which has allotted from \$50,000 to \$70,000 annually for this purpose, since 1941. The fund is administered by the Committee on Aid to Libraries in War Areas of the American Library Association. The ANNALS OF INTERNAL MEDICINE is one of the medical journals for which a number of subscriptions have been placed and several volumes of past issues since the outbreak of the war are being stored for later shipment. These volumes have been supplied at cost.

---

#### THE NEW YORK INSTITUTE OF CLINICAL ORAL PATHOLOGY

The first open meeting of the New York Institute of Clinical Oral Pathology will take place in Hosack Hall at the New York Academy of Medicine, New York City, October 30, 1944, at 8:15 p.m., the program to be devoted to a symposium on "Fluorine in Dental Public Health."

---

#### NEWS FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

The post of Assistant Surgeon General, to be filled by Brigadier General Raymond W. Bliss, has been created in a partial reorganization of the Surgeon General's Office. The Assistant Surgeon General will act for the Surgeon General in coördinating the work of the Operations Service, the various professional divisions, the Military Personnel Division and the activities of other divisions and services that affect operations.

A new Professional Administrative Service is created, with Colonel Arden Freer, F.A.C.P., as Chief and Colonel E. R. Long, Deputy Chief. It will include the following: Physical Standards Division, Nursing Division, Medical Statistics Division, Professional Inquiries Unit, Women's Health and Welfare Unit.

Major General George F. Lull, F.A.C.P., a member of the Committee on Physical Fitness of the American Medical Association, attended the Joint Committee on

Physical Fitness at Chicago, August 28. This conference represents the Army, Navy and civilian groups. The Committee on Physical Fitness was established by presidential order on April 29, 1943, to: (1) define and study problems relating to the promotion of physical fitness, in coöperation with national agencies and organizations, and encourage the development of coöperative programs for their solution; (2) serve as a center for the stimulation of State, district, and local programs for the promotion of physical fitness; (3) make available to States, localities, and organizations and agencies, upon request, the services of specialists in physical fitness; (4) prepare materials and serve as a clearing house on informational matters pertaining to the development of a national program of physical fitness.

Colonel James E. Ash, F.A.C.P., former curator of the Army Medical Museum, returned to his work July 25, after an extensive absence, during which he toured the North African theater of operation and sustained an eye injury which necessitated his evacuation to the Walter Reed General Hospital in Washington. His trip was taken to inspect the activities of the museum and Medical Arts Services which is collecting material for research and training in tropical diseases. The Museum is undertaking to supply all medical schools in the United States and Canada with material.

Colonel Ash now holds the appointment of Director of the Army Institute of Pathology, Army Medical Museum. This institute will serve as a central laboratory in pathology for all Army hospitals, including those in the theaters of operations. The material collected is available for research, teaching and historical purposes.

The Surgeon General's Office is seeking qualified men to become commissioned officers in the Sanitary Corps, and has announced the minimum requirements of enlisted personnel for appointment as second lieutenants. Applicants must have a bachelor's degree with an appropriate science major, and a minimum of two years experience in the particular field in which the applicant is qualified.

"Global Epidemiology," Volume 1 of a series on the geography of disease and sanitation covering particularly India, the Far East and the Pacific Area, will be published shortly. Brigadier General J. S. Simmons, F.A.C.P., Chief of the Preventive Medicine Service, Office of the Surgeon General, is one of the authors.

#### THE ARMY NURSE CORPS

The Army Nurse Corps, in conjunction with the Office of War Information, the Red Cross, the National Nursing Council for War Service, the War Manpower Commission, and the Recruiting Publicity Bureau of the Army, is making a concentrated effort to obtain 4,000 nurses by October. The need is urgent because of the increasing number of casualties.

A special treatment center for malaria and other tropical diseases has been opened at the Moore General Hospital, Swannanoa, N. C., by the Army Medical Department. It is under the command of Lt. Col. Joseph M. Hayman, F.A.C.P., of Cleveland, who has spent two years in the South Pacific studying tropical diseases. Lt. Col. Francis R. Dieuaide, F.A.C.P., Chief of the Tropical Disease Branch, Medical Division of the Surgeon General's Office, will administer the scientific phases of its activities.

## ATTENDANCE OF MEDICAL CORPS OFFICERS AT MEDICAL MEETINGS

Under date of February 24, 1941, the Adjutant General issued the following to all Army, Army Corps and Corps Area Commanders:

"You are authorized to permit officers of the Medical Corps under your jurisdiction who desire to attend meetings of any National Societies to do so on a detached service status and without expense to the Government, provided their services can be spared."

## THE WHOLE BLOOD PROGRAM OF THE SURGEON GENERAL

The first shipment of whole blood from the United States to soldiers wounded in France was made by the U. S. Army Medical Department by Army plane on August 21. Daily shipments have been made since—250 pints a day the first week, 500 pints a day the second week and 750 pints a day is the goal. Type "O" blood is being collected by the Red Cross for the shipments. The whole blood is prepared on the day it is drawn and 24 hours after it leaves the United States, it is available for transfusion in France.

Major Leon H. Warren, F.A.C.P., Chief of Research Coördination Branch, Technical Division, since February 4, 1944, has been promoted recently to Lieutenant Colonel.

---

Dr. George E. Baker, F.A.C.P., Casper, Wyo., has been appointed Acting Secretary of the Wyoming State Medical Society. Dr. Baker has recently completed the revision of the chapter on Rocky Mountain Spotted Fever for Tice's Practice of Medicine.

---

Dr. J. Warrick Thomas, F.A.C.P., who has been Head of the Department of Allergy of the Cleveland Clinic, Cleveland, Ohio, since January 1, 1939, is removing to Richmond to take over the practice of the late Dr. Warren T. Vaughn, and will be associated with Dr. W. Randolph Graham, F.A.C.P., in the establishment of the Vaughn Memorial Clinic, 201 West Franklin Street, Richmond, Va. His practice will be limited to Allergy and Internal Medicine. Dr. Thomas is a member of the Board of Regents of the American College of Allergists and Assistant Editor of their journal, *Annals of Allergy*.

---

Dr. E. David Sherman (Associate), Sydney, Nova Scotia, was retired from the Royal Canadian Army Medical Corps on June 10, 1944. He spent some time in postgraduate work in New York and Philadelphia and has now resumed practice at 327 Charlotte Street, Sydney. (Ed. Note: In Canada a retired officer is given an extra month's pay and extended the privilege of wearing his uniform.)

---

Dr. Jonathan C. Meakins, F.A.C.P., has retired September 7 from active service as Brigadier in the Royal Canadian Army and has resumed his work as Dean of McGill University Faculty of Medicine at Montreal.

---

Dr. Robinson Bosworth, F.A.C.P., Superintendent and Medical Director, Pleasant View Sanatorium, East St. Louis, Ill., was awarded the Hoyt E. Dearholt Memorial Medal for services in tuberculosis control in the Mississippi Valley Conference territory at the annual meeting of that Conference at Chicago, May, 1944.

NEW A.C.P. APPOINTMENTS DUE TO THE DEATHS OF DR. CHARLES HARTWELL COCKE  
AND DR. WILLIAM B. BREED, MEMBERS OF THE CREDENTIALS COMMITTEE

Two new appointments have been made until the next regular meetings of the Board of Regents and Board of Governors. Dr. Charles Fred Tenney, F.A.C.P., of New York City, will fill the vacancy caused by Dr. Cocke's death, as an appointee of the Board of Regents, and Dr. J. Edwin Wood, Jr., F.A.C.P., of the University of Virginia, will fill the vacancy caused by the death of Dr. Breed, as an appointee of the Board of Governors.

Dr. Chauncey W. Dowden, F.A.C.P., Louisville, Ky., heretofore Vice Chairman of the Board of Governors, will succeed to the chairmanship, succeeding Dr. Breed.

Dr. Reginald Fitz, Regent of the College, Boston, will attend to the ordinary duties of the College Governor for Massachusetts, including the endorsement of candidates, until a Governor to succeed Dr. Breed has been officially appointed.

Dr. George Morris Piersol, F.A.C.P., of Philadelphia, has been appointed to succeed Dr. Breed as the appointee of the American College of Physicians on the Committee on War-Time Graduate Medical Meetings.

---

Dr. William G. Leaman, Jr., F.A.C.P., has been made Associate Medical Chief of the Memorial Hospital, Roxborough, Pa.

---

Dr. William D. Stroud, F.A.C.P., is a member of the joint committee of the American<sup>o</sup> Medical Association and the National Committee on Physical Fitness, referred to under news items from the Surgeon General's Office. This joint committee is under the chairmanship of Colonel Leonard G. Rowntree, (MC), AUS, F.A.C.P., Chief of the Medical Division, National Selective Service.

---

The Twenty-second Annual Fall Clinical Congress of the Kansas City Southwest Clinical Society was held October 2-4, 1944, at Kansas City. Among the guest speakers were Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, "The Leukemias," "Changes in the Blood Due to Various Drugs, and a Consideration of Blood Transfusion Reactions," and "The Problem of Chronic Ulcerative Colitis"; Dr. Russell Haden, F.A.C.P., Cleveland, "Treatment of Rheumatoid Arthritis" and "The Treatment of Pernicious Anemia."

---

Under the direction of Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, the Chicago Institute for Hospital Administrators was held at the International House, University of Chicago, September 11-22, and sponsored by the American College of Hospital Administrators. The forenoons were devoted to lectures; the afternoons to seminars and field trips to selected hospitals for demonstrations; and the evenings, to conferences on administrative and departmental problems facing hospitals.

---

Lt. Col. Orpheus J. Bizzozero, F.A.C.P., Chief of the Allied Military Government's Health Section, recently reported that one in every five persons in Rome has tuberculosis, a situation attributed to nine months suffering under German occupation.

---

Metropolitan Life Insurance Company predicts that about the year 1950, diabetes will begin to outrank tuberculosis as a cause of death in this country. While deaths from tuberculosis in this country continue to decline, deaths from diabetes are progressively increasing. In 1909, the statisticians report that tuberculosis was the leading cause of death in this country, with diabetes ranking sixteenth. At the present

time, tuberculosis ranks seventh and diabetes ninth. The growing proportion of older people in the population plus the improvement in the fight against infectious diseases explains the change in rank of deaths from diabetes and tuberculosis.

---

Dr. Fred B. Clarke, F.A.C.P., Long Beach, Calif., and Dr. John Severy Hibben (Associate), Pasadena, are members of a joint committee composed of three members of the Los Angeles Bar Association and three members of the Los Angeles County Medical Association, which are sponsoring a program, "The Doctor Speaks to the Attorney," consisting of a series of lectures from September to December, covering varying legal medical problems.

---

Dr. Frank A. Trump, F.A.C.P., Ottawa, Kansas, is a Vice President of the Kansas Tuberculosis and Health Association.

---

Lt. Col. Arthur Parker Hitchens, F.A.C.P., has been retired from active service in the U. S. Army, and has been appointed Health Commissioner of Wilmington, Del. He is also Professor of Public Health and Preventive Medicine at the University of Pennsylvania School of Medicine.

---

Dr. Arthur H. Sanford, F.A.C.P., Rochester, Minn., has been reelected President of the American Board of Pathology. Dr. Howard T. Karsner, F.A.C.P., Cleveland, and Dr. Alvin G. Foord, F.A.C.P., Pasadena, have completed their two terms of service in the Board and have retired therefrom.

---

Dr. Miletus B. Jarman, F.A.C.P., Hot Springs, Va., addressed the American Congress of Physical Therapy at Cleveland, Ohio, September 6-9, on "Mineral Water Therapy; An Appraisal." Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the U. S. Army, was a guest speaker at the annual banquet.

---

Brigadier General Hugh J. Morgan, F.A.C.P., Director of the Medical Division, Brigadier General James S. Simmons, F.A.C.P., Chief of Preventive Medicine Service, Colonel William Paul Holbrook, F.A.C.P., representative of the Army Air Forces, and Colonel R. B. Skinner (Associate), representative of the Army Ground Forces are members of a committee appointed by the Office of the Surgeon General of the Army "to formulate plans for post-war training of medical corps officers who will be separated from the military service at the end of the war."

---

Dr. Emma S. Moss, F.A.C.P., New Orleans, Assistant Professor of Pathology and Bacteriology, Louisiana State University School of Medicine, has been elected Secretary-Treasurer of the Louisiana Association of Pathologists.

---

Dr. Francis E. Harrington, F.A.C.P., Minneapolis, will serve as the Acting Superintendent of the Minneapolis General Hospital until the appointment of a full-time Superintendent. He recently retired as Minneapolis Health Commissioner.

---

Dr. Theodore R. Van Dellen, F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School, is the lecturer in the medical science course in hospital administration, offered at the Northwestern University in the first semester of the current school term. There are five courses, in all, devoted to the history and development of hospitals, organization and management of hospitals, professional

services to the hospital patient, legal and political and sociological aspects of hospital administration and fundamentals of medical science.

---

Dr. William D. Robinson (Associate), of Vanderbilt University School of Medicine of Nashville, Tenn., has accepted an appointment as Assistant Professor in the Department of Medicine and Director of the Rackham Arthritis Research Unit of the University of Michigan Medical School, effective September 1.

---

Dr. Martin H. Collier, F.A.C.P., Grenloch, N. J., is President of the New Jersey State Department of Health.

---

Dr. Stockton Kimball, F.A.C.P., Buffalo, Associate in Medicine and Pharmacology at the University of Buffalo School of Medicine, was recently appointed Assistant Dean of the School.

---

The 94th Annual Session of the Medical Society of the State of Pennsylvania was held in Pittsburgh, September 19-21, under the presidency of Dr. Augustus S. Kech, F.A.C.P., Altoona.

A feature of the meeting was a panel discussion on clinical endocrinology by Dr. Charles W. Dunn, F.A.C.P., Philadelphia, Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., and Dr. Emil Novak, Baltimore.

---

Dr. Wingate M. Johnson, F.A.C.P., Winston-Salem, N. C., is President of the American Geriatrics Society. Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., is a Vice President.

---

Dr. Alvin L. Barach, F.A.C.P., New York City, addressed the Aero Medical Association at St. Louis, September 4-6, on, "Development of Pulmonary Active Tuberculosis as the Result of Aeroembolism at Simulated Altitudes above 40,000 feet."

---

Dr. Willard C. Rappleye, F.A.C.P., New York City, is a member of a committee headed by Dr. Arthur Bachmeyer of Chicago to make a survey of American hospitals and their post-war expansion needs. The survey will be financed by a grant of \$35,000 each by the Commonwealth Fund of New York, the National Foundation for Infantile Paralysis and the W. K. Kellogg Foundation. Hope is expressed that the study will determine the adequacy of distribution of present hospital facilities and the best method for ensuring adequate hospital care to all citizens.

---

#### AMERICAN BOARD OF INTERNAL MEDICINE EXAMINATIONS

The next written examination of the American Board of Internal Medicine will be held February 19, 1945, in various parts of the United States. The closing date for acceptance of applications for this examination will be December 15, 1944.

---

#### WAR-TIME GRADUATE MEDICAL MEETINGS AND KENTUCKY STATE MEDICAL ASSOCIATION MEETING COMBINED

On September 18-20, 1944, there was a combined meeting of the War-Time Graduate Medical Meetings and the Kentucky State Medical Association at Lexington, Ky. The Regional Meeting Committee of the War-Time Graduate Medical Meetings



consisted of Dr. Elmer L. Henderson, Chairman, Dr. Chauncey W. Dowden, F.A.C.P., and Dr. H. H. Shoulders. A number of Fellows of the College, including the following, participated in the program:

- Dr. John A. Toomey, Cleveland—"Chemotherapeutics in Pediatrics."  
Brig. Gen. Hugh J. Morgan, Washington—"The Medical Aspects of Penicillin" in a Symposium on Chemotherapy.  
Dr. William D. Stroud, Philadelphia—"Cardiovascular Diseases."  
Dr. Oscar O. Miller, Louisville—(Presidential Address). "Some Aspects of the Tuberculosis Problem."  
Dr. Roger I. Lee, Boston—"Accelerated Medicine Today and Tomorrow."  
Brig. Gen. James S. Simmons, Washington—"The New Weapons of Control of Insect-Borne Diseases."  
Dr. Ralph Pemberton, Philadelphia—"Arthritis."  
Col. John D. Youmans, Washington—"Nutrition—Its Relation to Deficiency Diseases."
- 

The Inaugural Meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia was held September 13, 1944, at which Dr. Eugene P. Pendergrass, F.A.C.P., retired as President and Dr. Charles L. Brown, F.A.C.P., was installed as President.

---

Dr. John T. O'Mara, F.A.C.P., Baltimore, has been reelected Secretary-Treasurer of the Board of Medical Examiners of Maryland.

---

Dr. Henry Boswell, F.A.C.P., Sanatorium, Miss., has been elected Vice President of the Mississippi State Hospital Association.

---

Dr. Francis G. Blake, F.A.C.P., Dean and Professor of Medicine, Yale University School of Medicine, with the assistance of his staff, and Dr. Samuel C. Harvey, Professor of Surgery at Yale, and his staff, conducted an afternoon symposium on penicillin medicine and surgery during the twentieth clinical congress of the Connecticut State Medical Society at New Haven, September 28-29.

---

Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the U. S. Army, was the principal speaker at the commencement exercises of the 1944 class at Northwestern University Medical School, September 14.

---

Dr. Carl H. Gellenthien, F.A.C.P., Valmora, N. M., will act as the New Mexico editor on the editorial staff of the *Rocky Mountain Medical Journal*, which has become the official journal of the New Mexico Medical Society.

Dr. Gellenthien was recently installed as President of the New Mexico Medical Society.

---

Dr. Lawrence Reynolds, F.A.C.P., Detroit, delivered the Caldwell-Carman Lecture before a joint meeting of the American Roentgen Ray Society and the Radiological Society of North America at Chicago, September 26.

---

Drs. R. M. Craig (Associate), Dayton, George X. Schwemlein (Associate), Cincinnati, and H. W. Kendell, Dayton, reserve officers in the U. S. Public Health Service, stationed at the Chicago Intensive Treatment Center, spoke on "Physiologic

Studies and Technics Employed During Fever-Chemotherapy of Early Syphilis" at the twenty-third annual meeting of the American Congress of Physical Therapy, Cleveland, September 6.

Major Maurice J. Abrams, F.A.C.P., (MC), AUS, recently returned from twenty-four months of duty overseas, where he was Chief of the Medical Service at one of the Army Hospitals in London. He is now on limited duty as Assistant Chief of Medical Service, Station Hospital, Fort Jackson, S. C. Major Abrams was formerly in practice at Brewton, Ala.

#### NEW YORK REGIONAL MEETING OF THE COLLEGE

The American College of Physicians conducted its first Regional Meeting for the State of New York in New York City, Friday, October 20, under the General Chairmanship of Dr. Asa L. Lincoln, F.A.C.P., Governor for Eastern New York, and with the coöperation and participation of Dr. Nelson G. Russell, Sr., F.A.C.P., of Buffalo, Governor for Western New York.

In the forenoon, members of the College were the guests of the New York Academy of Medicine, in connection with its Seventeenth Graduate Fortnight, at its Exhibit, which demonstrated recent advances in the etiology, pathology, diagnosis, prophylaxis and treatment of infections. The afternoon scientific session, at which Dr. Russell presided, was held at the New York Hospital and consisted of the following presentations: Dr. George Baehr, F.A.C.P., "Penicillin Treatment of Sub-acute Bacterial Endocarditis due to Enterococcus"; Dr. Homer Swift, "Recent Developments in Our Knowledge of Rheumatic Fever"; Dr. William C. Von Glahn, "Rheumatic Arteritis"; Dr. Ralph Boots, F.A.C.P., "Differential Diagnosis of Rheumatic Fever"; Dr. Arthur C. DeGraff, F.A.C.P., "The Cardiac Factor in Pneumonia"; Dr. Arthur J. Patek, Jr., "Liver Disease"; Dr. Walsh McDermott, "Penicillin Treatment of Syphilis"; Dr. George Wolff, "Current Treatment of Meningococcus Meningitis"; Dr. J. Casals, "A Current View of the Rabies Problem." Cocktails and dinner were served at the Waldorf-Astoria Hotel, following which the members were again the guests of the New York Academy of Medicine at a Panel Discussion on "Evaluation of Sulfa Drugs and Penicillin," Dr. David P. Barr, F.A.C.P., Chairman, and Drs. Rene J. Dubos, Colin M. MacLeod, John F. Mahoney, Frank L. Meleney and William S. Tillett members.

Dr. Mahlon Ashford, F.A.C.P., was Chairman of the Program Committee and Dr. Charles F. Tenney, F.A.C.P., was Chairman of the Committee on Arrangements.

Dr. R. H. Kampmeier, F.A.C.P., Nashville, has been appointed Acting Director of the Department of Medicine at Vanderbilt University School of Medicine.

#### OAK LEAF CLUSTER, DISTINGUISHED SERVICE MEDAL, AWARDED BRIGADIER GENERAL EDGAR ERSKINE HUME

Brigadier General Edgar Erskine Hume, F.A.C.P., has been awarded the Oak Leaf Cluster to the Distinguished Service Medal in recognition of service as Chief of the Allied Military Government Section, Fifth Army, in Italy, his citation reading, in part: "... he successfully carried out one of the most extensive military government tasks ever accomplished by the United States, being charged with the government of Campania, a region of 6,000,000 inhabitants including Naples, one of Italy's largest cities. He made detailed plans for the administration of Naples, which, under his orders, were put into immediate execution when the city was taken on Oct. 1, 1943.

"Despite enormous handicaps in Naples, where the Germans had destroyed the water supply, electric power sources, drains and other public utilities, had mined buildings, despoiled hospitals, dispersed the police and in general paralyzed the civil administration, he was able by his unusual ability and devotion to duty to restore order forthwith and within a few weeks to return the city's functions almost to normal. A threatened epidemic of typhoid was averted by his wise preventive measures. Our victory was thus hastened, as the army commander was free to perform purely military functions without the added burden of civil government.

"The respect in which this officer was held by the Italians, his intimate knowledge of the country, its people and language, and his rare administrative skill and leadership made him unique in his efficient handling of an extremely difficult and politically delicate task."

General Hume received the Distinguished Service Medal during World War I as Commissioner of the American Red Cross after the war in Serbia. He holds many academic degrees from American and foreign institutions and several decorations from foreign governments. He graduated from Johns Hopkins University School of Medicine in 1913, and has been a Fellow of the American College of Physicians since 1926.

Dr. Christopher G. Parnall, F.A.C.P., recently celebrated his twentieth anniversary as Medical Director of the Rochester General Hospital, Rochester, N. Y.

#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole.

##### *Mayo General Hospital, Galesburg, Illinois*

- October 18    High Blood Pressure
  - a. Pathological—Physiological Basis—Conservative Therapy—Renal Extracts
  - b. The Surgical Treatment
- November 1    Laboratory Diagnosis—and its relationship to treatment
  - a. Hypoproteinemia—Alkalosis—Acidosis—Dehydration—Electrolytic Balance
- November 15    Conditions Affecting Glucose Metabolism
  - a. Endocrine—Pituitary—Thyroid—Adrenal—Pancreatic
  - b. Renal, Alimentary, Hepatic. Diff. Diagnosis and Treatment

##### *Camp Ellis, Illinois*

- October 18    Diseases of the Intestinal Tract
  - a. Regional Ileitis, Colitis, Diverticulitis. Diagnosis and Treatment
  - b. Dysentery—Army and Bacillary
  - c. Malignancies
- November 1    Symposium on Organic Neurology
  - a. Central and Peripheral
- November 15    Dermatological Diseases
  - Clinic with Presentation of Cases and Slides. Diagnosis and Treatment.
  - a. The Less Common Venereal Diseases
    - Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid, Yaws—Slides—Diagnosis and Treatment

*Camp Grant, Illinois*

- October 18     Malignancies in the Army Age Group  
                   *a.* Melanomata  
                   *b.* Teratomata  
                   *c.* Lymphoblastomata
- November 1     Endocrinology  
                   *a.* Addison's Disease, Adrenal Cortex in Shock, Parathyroid Tetany, Traumatic Hypogonadism, Hypothyroidism, Hyperthyroidism, Post Traumatic Pituitary Syndrosis
- November 15     Virus and Rickettsial Diseases  
                   *a.* Virus Diseases  
                   *b.* Rickettsial Diseases

*Chanute Field, Rantoul, Illinois*

- October 18     Thrombosis, Thrombophlebitis and Anticoagulants  
                   *a.* Thrombosis, Thrombophlebitis and Embolism—Diagnosis and Treatment  
                   *b.* Heparin and Dicoumarol  
                       Action and Therapeutic Use
- November 1     Chronic Chest Diseases and Disease of the Larynx  
                   *a.* Tuberculosis, Pneumonoconiosis, Chronic Bronchitis, Bronchiectasis, Cysts, Fungus Infections, etc.  
                   *b.* Neoplasm—X-Ray and Surgical Treatment—Coccidioidomycosis and Allied Conditions  
                   *c.* Laryngeal Problems
- November 15     Head and Spine Injuries  
                   *a.* Methods of Diagnosis and Localization  
                   *b.* Do's and Don'ts before the patient reaches the special surgeon

*U. S. Naval Hospital, Great Lakes, Illinois*

- October 17     Immediate and Late Care of Urinary Tract Following Injury of the Spinal Cord and Bony Structures—Dr. Vincent J. O'Connor
- November 8     The Management of Acute Respiratory Obstructions—Dr. Paul H. Holinger

*Camp McCoy, Wisconsin*

- October 18     Dermatological Diseases  
                   Clinic with Presentation of Cases and Slides. Diagnosis and Treatment.  
                   *a.* The Less Common Venereal Diseases  
                       Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid, Yaws—Slides—Diagnosis and Treatment—Dr. G. A. Cooper
- November 1     Psychiatry, Psychoneurosis, Neurocirculatory Asthenia, Malingering, etc.—Dr. Lloyd H. Ziegler
- November 15     Malignancies in the Army Age Group  
                   *a.* Melanomata  
                   *b.* Teratomata  
                   *c.* Lymphoblastomata—Dr. Gorton Ritchie

*Truax Field, Wisconsin*

- October 18      Virus and Rickettsial Diseases  
                     a. Virus Diseases  
                     b. Rickettsial Diseases—Dr. Marcos Fernan-Nunez
- November 1    Peptic Ulcer and Gastritis  
                     a. Diagnosis and Medical Care  
                     b. Surgical Approach—Dr. Carl W. Eberbach

Note: War-Time Graduate Medical Meetings at Camp McCoy and Truax Field are arranged by the cooperating committee for Wisconsin. The members of this committee are Dr. Erwin R. Schmidt, Chairman; Dr. Elmer Sevringhaus and Dr. Francis D. Murphy.



DR. WILLIAM B. BREED  
 BOSTON, MASS.

### OBITUARIES

#### DR. WILLIAM B. BREED

Dr. William Bradley Breed, Chairman of the Board of Governors and ex officio member of the Board of Regents of the American College of Physicians, died after a short illness in Boston, Mass., on August 21, 1944, four days after his 51st birthday.

Dr. Breed had been a Fellow of the College since 1928, its Governor for Massachusetts since 1934. He rendered signal service to the College. At an early meeting of the College in Boston, 1929, he was Chairman of the

Entertainment Committee; at a later meeting of the College in Boston, 1941, he was General Chairman of the Session and the success of that meeting was due to him.

Dr. Breed's devotion to the College took many forms. He had been a member of the hard-working Committee on Credentials since 1935. He was Secretary-Treasurer of the joint committee of the American College of Physicians, the American College of Surgeons and the American Medical Association, on War-Time Graduate Medical Meetings from the inception of that Committee in 1943. The noteworthy achievements of this Joint Committee represented only a part of his war-time activities. He was one of the representatives of the College on the Joint Committee on Post-War Medical Service. In addition, he was a member, and in some instances chairman, of various committees in his State and in his community.

Dr. Breed was trained in medicine at the Harvard Medical School and at the Massachusetts General Hospital. While connected with other hospitals, most of his work was done at the Massachusetts General Hospital, where he was Physician and a member of its Executive Committee. He was also Associate in Medicine at Harvard Medical School.

Dr. Breed was primarily a clinician. He belonged, perhaps, to that diminishing group of great clinical internists, as contrasted with the specialists within internal medicine, or with the medical investigators.

Dr. Breed liked people and people liked Dr. Breed. So it was inevitable that he should have a large practice, both as a practitioner and as a consultant in internal medicine. He loved life, as he loved people, medicine and music. All of his talents were at the disposal of his patients and his friends. He had a genius for friendship. The American College of Physicians has lost more than a devoted Fellow, Governor and Regent—it has lost a beloved friend.

ROGER I. LEE, M.D., F.A.C.P.,  
Boston, Mass.

### DR. ISAAC JUDAH SILVERMAN

Dr. Isaac Judah Silverman, F.A.C.P., Washington, D. C., died at Georgetown University Hospital, August 6, 1944, aged 56.

Dr. Silverman was born in Calcutta, India, May 3, 1888; he attended Hawthorne College, Melbourne, Australia, and graduated from the University of Melbourne Faculty of Medicine in 1911, with the degrees of M.B. and Ch.B.; he did postgraduate work at the University of Melbourne and the Washington School of Psychiatry; he practiced medicine in Australia, New Zealand, Ontario, Canada, and in St. Joseph, Mo.

Dr. Silverman was appointed to the staff of the Gallinger Municipal Hospital, Washington, D. C., in 1929, and served as Instructor in Psychiatry at George Washington University School of Medicine from 1929 to 1933. He then became a member of the teaching staff at Georgetown University School of Medicine and advanced to Clinical Professor of Psychiatry and Assistant Chief Psychiatrist at Gallinger Municipal Hospital. He was a

member of the Medical Society of the District of Columbia and the American Psychiatric Association, and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1937. He was the author of "Psychical Function of the Cerebellum" and of many articles in medical journals. His death was caused by acute myocardial infarction (posterior) and arteriosclerotic heart disease.

WALLACE M. YATER, M.D., F.A.C.P.,  
Governor for the District of Columbia

### DR. LESTER DOW WATSON

Dr. Lester Watson, F.A.C.P., was a casualty of this war, ending his life as he would have preferred in wartime, on active duty in the service of his country.

He was born in Dorchester, Massachusetts, on May 14, 1901, a New Englander of many generations and with forbears who, by tradition, participated in all our struggles when the need arose. He graduated from Middlebury College in 1924 with the degree of B.S.; he received his medical training at Boston University where he graduated in 1928; he served his internship at the Massachusetts Homeopathic Hospital—later called the Massachusetts Memorial—and entered practice in Milton. He maintained a continued interest in hospital work and medical teaching, and, above all, was a public spirited citizen, devoted to the welfare of his community.

He was promoted to the rank of Visiting Physician at the Massachusetts Memorial Hospitals and to instructorship at his medical school; he was a visiting physician at the Milton Hospital and Convalescent Home; he examined for the tuberculosis division of the Boston Health Department; he lent a hand in Red Cross work, civilian defense plans, and Selective Service examinations; he was a conscientious member of the Massachusetts Medical Society, the American Medical Association, and the College (Fellow, 1942); and, in addition, he was an active practitioner—a fine type of physician, alert, unselfish, competent, and beloved.

When war broke out he felt that he must play some part in it. He obtained a commission in the Public Health Service, entering on active duty in September 1943. He died on July 14, 1944, after a sudden and brief illness. He leaves his wife, Mrs. Dorthy P. Watson, and two sons.

REGINALD FITZ, M.D., F.A.C.P.,  
Regent.

### DR. WILLIAM STIMPSON HUBBARD

Dr. William Stimpson Hubbard, F.A.C.P., for many years an internist of Brooklyn, N. Y., died September 1, 1944, at the home of his daughter, Miss Ruth W. Hubbard, in Philadelphia, where he had lived since his retirement nine years ago.

Dr. Hubbard was born in Claremont, N. H., September 20, 1886. He attended the Holderness School for Boys at Plymouth, N. H.; received his

A.B. degree from Trinity College, Hartford, Conn., in 1888, and his M.D. degree from the Long Island College Hospital in 1894. A part of his medical training was received at the University of Michigan. For thirty years he was Assistant Attending Physician and Chief of the Medical Service, respectively, of St. John's Hospital, and a Visiting Physician to the Kings County Hospital, in Brooklyn. He had also served as Visiting Physician to the House of St. Giles the Cripple, and Consulting Physician to the John T. Mather Memorial Hospital at Port Jefferson, N. Y.

He had been a member of the Brooklyn Society of Internal Medicine, Medical Society of the County of Kings, the New York State Medical Society and the American Medical Association. He became a Fellow of the American College of Physicians in 1931 and maintained an abiding interest in the College and its activities throughout the remainder of his life. During his retirement in Philadelphia he was a frequent visitor at the College Headquarters. His was a long life of unselfish service to the profession and to the public.

#### DR. JAMES W. SCOTT

Dr. James W. Scott, Associate, died in the Mount Carmel Mercy Hospital, Detroit, June 25, 1944, at the age of seventy-five, of myocarditis.

Dr. Scott was born July 1, 1868, in Lancastershire, Scotland. His early training was received in Scotland, whereupon he came to America and received his medical education at the Michigan College of Medicine and Surgery, graduating in 1896. He later did post-graduate study in Glasgow and Edinburgh, Scotland. He had been a member of the Michigan State Medical Society and the American Medical Association and was an Associate of the American College of Physicians since 1920, by virtue of membership in the old American Congress on Internal Medicine, which was merged with the College in 1926, its members becoming Associates of the College.

#### DR. CHARLES EDWIN HOMAN, JR.

Dr. Charles Edwin Homan, Jr., F.A.C.P., Medical Director of the Ochsner Clinic, died in New Orleans on July 25, 1944, of coronary thrombosis.

Dr. Homan was born in Bibb County, Georgia, July 18, 1898. He received the Bachelor of Science degree from Mercer University in 1918, and the Doctor of Medicine degree from Johns Hopkins University in 1923; he interned at the Allegheny General Hospital from 1923 to 1924.

For several years he practiced in Chattanooga, Tennessee, where he was a member of the staffs of the Baroness Erlanger Hospital and the Pine Breeze Sanatorium, and Director of the Outpatient Department of the former institution. In 1932 he became Assistant Medical Director of the Mutual Life Insurance Company, Hartford, Connecticut. He became Medical Director of the Ochsner Clinic in January, 1943.

Dr. Homan had been a Fellow of the College since 1930. He was a



member of the Orleans Parish Medical Society, the Louisiana State Medical Society, and the American Medical Association.

EDGAR HULL, F.A.C.P.,  
Governor for Louisiana

### DR. LOUIS LEROY

Dr. Louis Leroy, F.A.C.P., died at his home at Memphis, Tenn., May 9, 1944. Dr. Leroy was born in Chelsea, Mass., 1874, received his B.S. at the University of Nashville and studied medicine at the University of Kentucky and at the Medico-Chirurgical College of Philadelphia, graduating from the latter in 1896.

From 1900 to 1906, he was a member of the faculty of the Vanderbilt University School of Medicine, attaining the rank of Professor of Pathology and Bacteriology. In 1906, he became Professor of Medicine at the University of Tennessee College of Medicine, an appointment which he held to the time of his death. He served at one time as President of the Tennessee State Board of Health, as Nashville City Bacteriologist and as the Tennessee State Bacteriologist. He was a member of the Memphis and Shelby County Tuberculosis Commission for many years. He was formerly Vice President of the Tennessee State Medical Association and at one time, a member of the House of Delegates of the American Medical Association. He was a member of the United States Coast Guard Auxiliary.

Dr. Leroy joined the American College of Physicians in 1920, having been sponsored by the late Dr. Lewellys Barker and the late Dr. William S. Thayer, both of Baltimore.

Aside from the regular practice of medicine, Dr. Leroy followed, almost as a hobby, the study of medico-legal medicine. He enjoyed appearing in court as an expert witness, and became very proficient in this work. However, his great hobby was the Mississippi River. He probably knew as much about the history of this great River in the vicinity of Tennessee as any one who has ever lived. He knew its peculiarities, understood its treacherous nature and kept up with its ever changing channels. His greatest pleasure was to pilot a boat on the Mississippi.

During the flood in 1937, Dr. Leroy directed the Red Cross rescue work from Cairo, Ill., to Rosedale, Miss. The fleet of boats that assisted him worked night and day and rescued hundreds of families that were shut off from escape by the rising waters.

It is, indeed, difficult to understand how Dr. Leroy found time to do so much, yet he was thorough and intense in everything he did. He was a great reader, not limiting himself to medicine alone. He was widely informed on guns, pistols, and was a student of game and wild life in the Southern States. Those who knew him well were amazed at the detailed information that he could give on almost any subject.

The South has lost a good man, a great scholar and an intelligent physician.

WILLIAM CALVERT CHANEY, M.D., F.A.C.P.,  
Governor for Tennessee

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 21

NOVEMBER, 1944

NUMBER 5

---

## DIFFERENTIAL DIAGNOSIS OF TERMINAL GLOMERULONEPHRITIS AND MALIGNANT HYPERTENSION. I. RENAL ASPECTS\*

By A. C. CORCORAN, M.D., and IRVINE H. PAGE, M.D., F.A.C.P.,  
*Indianapolis, Indiana*

DIFFERENTIAL diagnosis in patients showing severe renal damage from chronic glomerulonephritis on the one hand, and malignant hypertension on the other has always been difficult. At this stage the two conditions have in common the clinical pattern of hypertension, loss of weight, anemia, so-called "albuminuric retinitis," depressed renal function, azotemia, proteinuria and increased organized urinary sediment. Indeed, at least cases 1 and 8 of Bright's original report and cases 1, 5 and 8 of his second paper in Osman's edition<sup>1</sup> seem to us instances of hypertension, essential or malignant rather than the characteristic syndrome, glomerulonephritis, which now most characteristically bears his venerated name.

We selected for study two groups of patients who had in common the evidences of disease noted above and who had not, at the time of first observation, progressed to uremia with its coma, acidosis and jactitation. We shall present with others in the succeeding reports of this series diagnostic criteria based on (a) the study of the heart and (b) of the general clinical course of this group. Criteria selected from the cardiac or anamnestic segments of the total pattern will be shown to permit the establishment of a correct diagnosis in most instances. The purpose of the present report is to direct attention to criteria for diagnosis derived from studies of renal function. We shall show that in certain cases the diagnosis may be confidently established from these alone.

*Methods, Terminology, Their Evaluation.* The methods of renal functional study used were (1) determination of plasma inulin and diodrast clearances and of maximum tubular secretory capacity for diodrast (T<sub>mp</sub>),

---

\* Received for publication February 3, 1944.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Indiana.

(2) urea clearance, (3) determination of maximum urinary non-protein specific gravity, (4) proteinuria, and (5) counts of urinary sediment.

Clearances of diodrast and inulin and Tmp were determined during intravenous infusion of these substances in patients whose urine was collected by catheterization and bladder washing. The methods used are similar to those described by Smith, Goldring and Chasis.<sup>2</sup> Each of the values reported in this communication is the mean of three satisfactory periods of urine collection. The measurements of diodrast-iodine and inulin were made as described by Corcoran and Page.<sup>3, 4</sup>

Since these methods are not in general use and since also their evaluation is not settled, we append the following review of the significance we attach to them.

*Inulin Clearance.* Plasma inulin clearance is a satisfactory measure of glomerular filtration rate in normal animals and in man (Smith<sup>5</sup>). Neither our own experience nor a review of the literature gives any indication that this relationship fails in terminal Bright's disease or malignant hypertension with renal failure. Consequently, in this report we shall accept plasma inulin clearance as the equivalent of the rate at which water and substances dissolved in this water are filtered through the glomerular capillaries.

*Diodrast Clearance.* Diodrast, dissolved in plasma water and in small measure bound by plasma albumin (Smith and Smith<sup>6</sup>), distributes itself throughout the interstitial fluids of the body. Renal tubular cells, presumably of the proximal convoluted tubule, possess a mechanism which readily and efficiently transfers diodrast or a variety of similar substances from interstitial to tubular fluid, whence it is excreted, apparently without tubular reabsorption. In addition, a fraction (about 0.15) of the plasma diodrast is filtered through the glomeruli into tubular fluid. The combined effect of filtration and secretion is that the renal venous diodrast level is very low or, in other words, the renal extraction of diodrast (percentile arteriovenous difference) is nearly complete. This, at least, is the situation in dogs (White and Heinbecker,<sup>7</sup> Corcoran, Smith and Page<sup>8</sup>) and there are compelling reasons for supposing that the same is true in normal man (Smith<sup>9</sup>). The small residue of diodrast in the renal venous plasma is there in part because some of this plasma is constituted of blood which nourished non-excretory renal tissue; in part also because of the equilibrium which must obtain between venous capillaries and interstitial fluid (Corcoran and Page<sup>10</sup>). The net effect is that the removal of diodrast from the area of interstitial fluid which directly bounds actively secreting tubules is complete.

Plasma clearance is the volume of plasma whose content of a substance is equivalent to the amount of that substance (in this discussion, diodrast) which appears in one minute's urine. Where the proportion of a substance cleared from plasma is less than 100 per cent, then the plasma clearance is correspondingly less than total renal plasma flow. But, when, as in the case of diodrast, the excretory tissues virtually remove all of it, then plasma

clearance may be regarded as the close equivalent of effective renal plasma flow, using the word "effective" to indicate the perfusion of excretory tissue. This equivalence, proposed by Smith, Goldring and Chasis,<sup>2</sup> we adhere to for reasons stated above, neglecting, because of its small influence on clearance, the contribution to urinary diodrast made by diodrast removed from red blood cells.<sup>7, 8</sup>

The equivalence of plasma diodrast clearance and effective renal plasma flow, valid under normal conditions, must be examined for its significance in the diseases with which we are here concerned, and first, experimentally. In published (Corcoran and Page<sup>11</sup>) and unpublished observations on dogs with experimental renal hypertension, due either to compression of the renal artery by a clamp or to experimental perinephritis, we have not observed failure of diodrast extraction, or of the analogously excreted material, phenol red, in the absence of uremia or of renal necrosis. On the contrary, the extraction of these substances from plasma by the kidneys was maintained in spite of wide variations of renal plasma flow. The equivalence of diodrast clearance and effective renal plasma flow is therefore maintained in experimental renal hypertension, and the analogy may be drawn to malignant hypertension in human beings. In experimental glomerulonephritis (Fouts, Corcoran and Page<sup>12</sup>) phenol red extraction was observed to decrease in the presence of severe injury; but this change was associated with concurrent depression of inulin extraction, and we have concluded that, as regards the residually functioning nephrons, extraction was presumably well maintained. This observation also may be extended to glomerulonephritis in human beings.

The equivalence of plasma diodrast clearance with effective renal plasma flow is invalid in conditions of widespread tubular renal injury, such as is caused by uranium (Bobey, Longley, Dickes, Price and Hayman<sup>13</sup>) or tartrate (Nicholson, Urquhart and Selby<sup>14</sup>) where the capacity of renal tubules to secrete is depressed while these tubules retain their connection with functioning glomeruli. Nephrons such as these Smith<sup>9</sup> refers to as "impotent." Findley, Edwards, Clinton and White<sup>15</sup> have suggested that such tubules may occur widely in the kidneys in hypertension, that they would decrease diodrast extraction and result in a level of plasma diodrast clearance less than true effective renal plasma flow. Smith,<sup>16</sup> and Goldring, Chasis, Ranges and Smith,<sup>17</sup> starting from a similar premise as regards tubular injury, view it as most probable that diodrast will diffuse in renal interstitial fluid from an injured tubular boundary to an adjacent intact tubule, where it can be secreted. The net effect in this latter instance is a level of plasma diodrast clearance greater than true effective renal plasma flow. For this phenomenon as it occurs in conditions of tubular injury we (Corcoran, Taylor and Page<sup>18</sup>) have proposed the term "vicarious clearance." That this process occurs in essential hypertension has been suggested by Goldring, Chasis, Ranges, Bradley and Smith.<sup>9, 19</sup> Their evidence cannot here be

considered in detail; it suffices to note that (a) the phenomenon is not uniform, even in hypertensives showing renal injury and (b) as Smith<sup>19</sup> has indicated, the discrepancy introduced into the equivalence of plasma diodrast clearance and renal plasma flow is not very great. For these reasons, we regard plasma diodrast clearance as the equivalent of effective renal plasma flow in malignant hypertension.

As we have indicated, in experimental glomerulonephritis there is reason to suppose that diodrast clearance would in fact measure effective renal plasma flow. The renal structural changes of glomerulonephritis in human beings are characteristically quite opposite to the condition of intact glomerulus and injured tubule which vitiates the relationship of diodrast clearance and effective renal plasma flow in toxic nephrosis. Consequently, except for unusual circumstances indicated below, we accept plasma diodrast clearance as the equivalent of effective renal plasma flow in clinical glomerulonephritis.

*Filtration Fraction.* Having thus reviewed the facts which lead us to regard inulin clearance as a measure of glomerular filtration rate and plasma diodrast clearance as the equivalent of effective renal plasma flow in the two diseases with which we have to deal, it follows that, in these conditions, as in normal circumstances, the volume of filtrate formed per cubic centimeter of plasma flowing through glomeruli may be taken as glomerular filtrate/plasma flow or inulin/diodrast clearance. This value is known as "filtration fraction." The hydrostatic factors which determine the volume of filtrate formed per c.c. of effective renal plasma flow have been discussed by Lampion<sup>20</sup> with regard particularly to renal arteriolar resistance. Normally, these include the arterial pressure, the resistance of afferent and efferent glomerular arterioles, intrarenal and intracapsular pressure and the osmotic pressure of the plasma proteins. In disease, but not in health, the factor of plasma protein concentration may become a highly significant variable, for hypoproteinemia is common in terminal Bright's disease and, as we shall show, is not infrequent in malignant hypertension with renal failure. Hypoproteinemia, by lowering plasma osmotic pressure, decreases the resistance to filtration and thus would, other factors being equal, increase filtration fraction. We have, therefore, found it desirable to calculate from Lampion's<sup>21</sup> figures 1 and 2 a value we term, "Corrected Filtration Fraction," and abbreviate as  $F^S=7.0$ . By it, we mean the level which filtration fraction would reach, if, other factors being equal, the patient's serum protein pressure were normal (26.4 mm. Hg). This osmotic pressure is taken as that which corresponds to a serum total protein content (abbreviated as S) of 7.0 gm. per 100 c.c. with albumin/globulin ratio 2.2. The normal value of corrected filtration fraction equals that of filtration fraction in normal people; in disease, its deviations from this normal indicate the theoretical effectiveness of glomerular filtration as it would be with the variable of serum protein content removed. The comparison of corrected filtration fraction with the observed level of filtration fraction indicates the extent to which variations of serum

protein content have influenced the capacity of the glomeruli as filtering beds. A low level of this value indicates that either the hydrostatic pressure in the glomerular capillaries is low or that the capillaries are themselves in large measure impermeable to filtration. A high level of this function indicates increased intraglomerular hydrostatic pressure. The further significance of this concept in the interpretation of functional changes in renal disease we shall communicate elsewhere.

Unfortunately, as we shall show, this function is not calculable in all the patients with whom we deal, since in some it leads to a negative number. To include these latter in our data, while avoiding a concept such as that of negative filtration, we have calculated by Lampport's methods the apparent terminal glomerular serum osmotic pressure and determined the difference in mm. Hg between this value and normal serum osmotic pressure. This pressure difference, abbreviated as  $DP_o^s$ <sup>7</sup> indicates, when positive, the effective head of filtration pressure at normal level of proteinemia, and, when negative, indicates the extra pressure which would have to be applied to establish filtration at normal levels of proteinemia. The relation between positive values of this function and corrected filtration fraction is shown in figure 1, as obtained from Lampport's calculations.

*Tubular Secretory Mass ( $Tm_D$ )*. The diodrast excreted by secretion in the urine is determined by finding the urinary minute excretion of diodrast and subtracting from this value the diodrast present in urine as the result of filtration. This value, expressed in milligrams of diodrast (determined as iodine) is known as  $T_D$ . As the amount of diodrast brought to tubular cells in the blood is increased, a point is reached at which the cellular transfer system is saturated. The amount excreted by secretion at this point rises to a maximum ( $Tm_D$ ) which is not altered by increasing still further the plasma diodrast concentration.

Until the point of tubular saturation is reached, i.e., as long as  $T_D$  is less than  $Tm_D$ , the renal extraction of diodrast remains normally at a maximum, as does likewise the level of plasma diodrast clearance. When, in normal kidneys, the amount of diodrast brought to them for excretion (renal blood flow  $\times$  blood diodrast content) is large enough to saturate the cells,  $Tm_D$  is reached, the tubules are uniformly saturated, their percentile extraction of diodrast from blood decreases and clearance is therefore depressed. The measurement of  $Tm_D$  made in such circumstances is a measurement of one aspect of tubular functional capacity, viz., secretion. But, since the capacity to secrete must be considered uniformly distributed in the cells specialized to this function in every nephron, it follows that this measurement of maximum secretory activity is a measure of functioning tubular mass. The principle of measurement is that of counting the cars of a railroad in terms of the coal they can carry.

The high blood levels of diodrast necessary to saturate the tubules of normal kidneys do not ordinarily alter the rate of glomerular filtration.

Inulin clearance is, therefore constant and, diodrast clearance being depressed, the filtration fraction (inulin/diodrast clearance ratio) rises.

Were the kidney to be more severely injured in some large areas than in others, the damaged areas, impotent as regards secretion, would saturate when the diodrast "load" (amount presented to the cells for secretion per minute) was yet small, while in the better preserved areas of structure saturation would not yet be accomplished. Titration of secretory capacity by slowly increasing plasma diodrast concentration in normal patients and in some patients with hypertension has shown that such inequality of tubular activity is of minor degree (Smith<sup>9</sup>). That large variations in the degrees of focal tubular saturation occur in terminal glomerulonephritis is indicated by observations made in patients Nos. 5, 8 and 10 of this group. In these, as we shall show, plasma diodrast clearance was depressed and filtration fraction thereby increased at a ratio of  $T_D/T_{mD}$  of about 0.3. We interpret this as signifying that certain tubular areas, presumably the most damaged, were fully saturated as regards secretory capacity at a time when two-thirds of the kidneys' capacity for secretion remained still unsaturated. This gross inequality of tubular secretory capacity we provisionally term "Focal Tubular Saturation." The explanation for its presence seems to be (1) the presence of tubular areas whose small residue of secretory capacity is saturated at even low renal loads of diodrast and (b) around which fibrosis prevents the escape of the diodrast in interstitial fluid to other relatively intact tubules.

*Urea Clearance.* The normal significance of urea clearance and its clinical value in Bright's disease have been reviewed in the monograph by Van Slyke and co-workers<sup>22</sup> and widely elsewhere. We need only here note that urea is normally excreted as the result of filtration and subsequent partial reabsorption. Under normal conditions and at levels of urine flow customary during the measurement of maximum urea clearance ( $C_m$ ) the proportion of urea reabsorbed is relatively constant at about 50 per cent. The significant physiological variable in urea clearance is therefore the rate of glomerular filtration. Abnormally, in advanced Bright's disease, the reabsorption of urea may be somewhat decreased (Chasis and Smith<sup>23</sup>) but the effect is not usually a large one in the stage with which we deal here and the general parallelism of urea clearance and glomerular filtration rate is well maintained.\*

*Concentration Test.* Ever since urinalysis passed from the phase of urinoscopy, the power of the kidneys to form urine of high specific gravity

\* For many of the determinations of urea clearance and serum protein recorded in this report we are indebted to Dr. O. M. Helmer of this laboratory. We wish to acknowledge the technical assistance of Mr. Ora Harvey in these analyses. In every instance urea clearance was determined as the clearance of urea + urinary ammonia. The methods used by Dr. Helmer were, for urea determination, the urease aeration-titration of Van Slyke and Cullen and, for protein determination, micro-Kjeldahl digestion and Nessler colorimetry. The other determinations were, in the case of urea, made by the manometric hypobromite method of Van Slyke and Kugel and, in the case of protein, by biuret colorimetry. The change in methods does not involve any change in the data.

has been one of the simplest demonstrations of normal renal function. Practiced under controlled conditions, as is obtained in the Addis<sup>24</sup> or similar tests, the measurement provides a semi-quantitative index of renal injury. Its significance in Bright's disease has been reviewed by Alving and Van Slyke<sup>25</sup> and, with regard to hypertension, briefly by Corcoran and Page.<sup>26</sup> It will suffice here to observe that (1) urinary non-protein maximum specific gravity does not decrease progressively after it has reached a level near 1.010, although (Hayman, Martin and Miller<sup>27</sup>) the number of functioning nephrons continues to decrease. This apparent paradox is satisfactorily explained by Newburgh<sup>28</sup> in terms of the renal osmotic work. (2) In hypertension there is a general parallelism of concentrating power and  $Tm_D$ ; concentrating power tends to be proportional to  $Tm_D$  and inversely proportional to some function of filtration rate.<sup>26</sup> This relationship in hypertension and Bright's disease will be the subject of a later communication.

## RESULTS

The observations of renal function and calculations made from them are summarized in tables 1, 2 and 3.

*I. Differentiation of Malignant Hypertension with Renal Failure and Terminal Bright's Disease: Data of table 1.* For convenience in presentation, we have calculated together with the data from the individual cases the means of the data from the patients in each group. We shall consider first the broad points of difference indicated by these means.

The nearly equal levels of renal blood flow (HD) and plasma diodrast clearance (DC) in the two groups accord with our impression that the clinical status of the patients in the two groups were comparable. A difference appears first in the levels of plasma inulin clearance (IC), the mean in terminal glomerulonephritis being nearly half that of the malignant hypertensives with renal failure. The higher inulin clearance in the hypertensives with nearly equal rates of plasma diodrast clearance results in a high filtration fraction (FF) in patients of this group. The mean filtration fraction recorded in Bright's disease is within the normal range ( $0.19 \pm 0.024$ ).<sup>9</sup>

Another wide difference is shown in the mean levels of tubular secretory capacity ( $Tm_D$ ) which, in terminal glomerulonephritis, is less than half the value found in malignant hypertension. The higher level of  $Tm_D$  in the hypertensives with a rate of effective renal blood flow approximating that of glomerulonephritis results in a low mean value for the rate of effective renal blood flow per unit of functioning tubular mass ( $HD/Tm_D$ ). In these malignant hypertensives, the residual tubular mass is thus shown to be definitely ischemic, while it is, if anything, hyperemic in terminal glomerulonephritis. That the renal ischemia present in the malignant hypertensives is due to increased renal vascular resistance greater than that in glomerulonephritis is emphasized by the higher level of arterial pressure in the hypertensives.



The expected low values of serum total protein and albumin content were found in patients suffering from glomerulonephritis; not as generally recognized is the frequent (five out of 10) occurrence of hypoproteinemia in malignant hypertension with renal failure. Similarly, the low hematocrit level in Bright's disease reflects the anemia characteristic of this condition in its terminal phase; that the hematocrit index should be nearly as low in malignant hypertension with renal failure was unexpected. The slightly lower hematocrit index of the nephritics resulted only in a somewhat lower level of effective renal blood flow for an equivalent rate of renal plasma flow;

TABLE I  
Measurements of Renal Function in Terminal Bright's Disease  
and in Malignant Hypertension with Renal Failure

No.	Init.	HD	DC	IC	FF	Tm <sub>D</sub> mg. D-I per min.	HD/Tm <sub>D</sub> c.c. per min.	T.P.	Alb.	Hem. per cent	Pm. mm. Hg	DP <sub>0</sub> S <sup>-7</sup>
		c.c. per 1.73 sq. m. per min.						gm. per 100 c.c.				
A. Terminal Bright's Disease												
1	Fi.	191	130	22.2	0.17	9.2	20.7	4.6	3.2	32	154	-7.12
2	Mi.	138	92	17.6	0.19	7.15	19.3	5.5	3.8	34	155	-1.22
3	We.	70.3	50.6	13.4	0.26	2.68	26.7	6.4	3.7	29	141	4.58
4	Wi.	80.3	53.8	14.2	0.26	2.2	36.5	4.6	3.0	34	114	-6.53
5	Hu.	(31.1)	(23)	11.4	(0.5)	2.1		5.8	3.7	27	141	
6	Hi.	49.6	38.3	5.4	0.14	1.7	29.2	6.9	4.8	23	149	6.86
7	Sm.	25.1	17.3	4.5	0.26	0.8 <sub>3</sub>	31.2	4.3	1.5	32	147	-13.7
8	Ha.	(12.6)	(10)	3.9	(0.4)	0.6		6.1	4.0	20	157	
9	Co.	40.2	32.2	8.9	0.28	0.437	92	5.5	3.9	20	150	5.12
10	Fr.	(9.8)	(8.0)	3.1	(0.4)	0.32		5.7	3.8	18	124	
Mean*		85	59	12.3	0.22	3.45	36.5	5.5	3.5	27	143	-1.7
B. Malignant Hypertension with Renal Failure												
1	Ed.	163	116	28.3	0.28	11.27	14.96	6.7	4.2	29	189	13.8
2	Gr.	165	117	34.6	0.30	10.9	15.13	7.8	4.5	29	182	22.63
3	La.	82	47	18.5	0.39	8.62	9.4	5.6	3.7	42	162	14.88
4	Ho.	136	88	29.3	0.33	8.6	15.9	7.1	4.6	35	159	17.11
5	Mk.	109	73	20.3	0.28	8.1	13.4	6.4	4.1	33	159	10.16
6	Co.	98	60	23.4	0.40	7.8	12.6	5.7	3.8	39	163	17.15
7	Ar.	121	85	23	0.27	7.6	15.96	4.8	3.4	30	176	1.66
8	Re.	66.7	44.7	14	0.30	7.05	9.5	7.0	4.3	33	189	17.33
9	Ch.	75	50	15	0.29	5.9	12.7	5.5	2.9	33	213	-1.42
10	He.	88	56	16	0.29	4.5	19.6	5.5	4.5	36	180	11.28
Mean		110	74	22.2	0.31	8.0	13.9	6.2	4.0	33	179	+12.50

Renal function in terminal glomerulonephritis and malignant hypertension with renal failure, arranged in order of descending values of Tm<sub>D</sub> per 1.73 square meters of body surface. Init.: initial letters of patient's surname; HD, effective renal blood flow; DC, plasma diodrast clearance; IC, plasma inulin clearance; FF, filtration fraction; Tm<sub>D</sub>, maximum tubular secretory capacity for diodrast, mg. diodrast-iodine per minute. HD/Tm<sub>D</sub>, effective renal blood flow per unit of Tm<sub>D</sub>; T.P., serum total protein; Alb., serum albumin, gm. per 100 c.c.; Hem., hematocrit index, per cent; Pm., mean of systolic and diastolic arterial pressure. DP<sub>0</sub><sup>S-7</sup> is the difference in mm. Hg between presumptive terminal osmotic pressure of patient's serum in glomeruli and normal serum osmotic pressure when S, i.e., serum total protein of albumin/globulin ratio 2.2, equals 7.0 gm. per 100 c.c.

TABLE II  
Demonstration of Focal Tubular Saturation in Terminal Glomerulonephritis

No.	In.	Plasma Diodrast- Iodine mg. per 100 c.c.	Plasma Diodrast Clearance c.c. per min.	T <sub>D</sub> (T <sub>mp</sub> ) mg. D-I per min.	Filtration Fraction	HD/T <sub>mp</sub> c.c. per min.	T <sub>D</sub> /T <sub>mp</sub>
5	Hu.	4.0 26.0	23 18.4	0.5 (2.1)	0.5	14.7	0.24 (1.0)
6	Ha.	2.6 25.0	10 5.7	0.2 (0.6)	0.4	21	0.33 (1.0)
10	Fr.	1.8 4.5 16.0	8.0 7.1 3.1	0.1 0.21 (0.38)	0.4	30.5	0.26 0.55 (1.0)

No. and In. as in table 1. Each value shown is the mean of those observed during three periods of urine collection. The high initial values of Filtration Fraction and low relative levels of diodrast clearance and HD/T<sub>mp</sub> indicate that renal diodrast extraction was depressed at the lowest level of plasma diodrast concentration observed in each case. Since, at this time, the amount of diodrast secreted (T<sub>D</sub>) was less than the maximum (T<sub>mp</sub>) (the latter indicated in brackets under its heading) the conclusion is drawn that in focal areas tubules were saturated while others were not.

this as we have seen, is countered in a degree by the high rates of effective renal blood flow per unit of residually functioning tissue in these patients.

The effects of the differences in serum protein level are much more significant than those due to anemia. They are reflected in the values obtained for Corrected Filtration Fraction and its equivalent  $DP_0^S=7$ . In four of seven nephritics and one of 10 hypertensives, it appears that filtration would have ceased had serum protein been normal. Averaging the pressure differences algebraically, a negative value is obtained from the nephritics, indicating that filtration would not have occurred in the group had there not been hypoproteinemia. A positive value, at about the normal level, is obtained from the mean of the levels in the hypertensives.

To summarize these differences between the means observed in the two conditions, while also restating them in terms of their probable physiological equivalents, we note that (1) the rates of effective renal blood and plasma flow are nearly equal in patients with terminal Bright's disease and those with malignant hypertension and renal failure; the means are somewhat lower in the nephritics because no patient with malignant hypertension was found with effective renal plasma flow lower than 40 c.c. per minute whereas three such occurred among the terminal nephritics. (2) The rate of glomerular filtration is much lower among the nephritics; it was less than 15 c.c. per minute in eight of the nephritics and in only one of the hypertensives. (3) The coincidence of a lower filtration rate and nearly equal rate of effective renal plasma flow in the nephritic group results in their maintaining a mean level of filtration fraction lower than that of the hypertensives, i.e., the nephritics' tubules are presented with less glomerular filtrate than are those of the hypertensives. However, whereas the mean level of filtration frac-

TABLE III

Comparison of Generally Available Methods of Measuring Renal Function in Terminal Glomerulonephritis and Malignant Hypertension with Renal Failure

No.	Init.	Urea Clearance per cent of normal	Blood Urea N mg. per 100 c.c.	Proteinuria gm. per 24 hours	Maximum Specific Gravity	Urinary R.B.C.	Sediment Casts
						1000's per 24 hrs.	
A. Terminal Glomerulonephritis							
1	Fi.	11.6	38.6	2.5	1.014	330	27
2	Mi.	13.5	31.6	3.8		189	0.0
3	We.	11.3	42.8	10.6	1.009	197	0.0
4	Wi.	9.4	57.6	8.0	1.015	296	0.0
5	Hu.			4.9			
6	Hi.	4.9	80.5	7.1	1.017	367	20
7	Sm.			12.5	1.009		
8	Ha.	4.35	133	0.04	1.0095	1690	0.4
9	Co.	9.8	87	15.9	1.0125	880	10.4
10	Fr	5.1	133	2.5	1.010	1350	5.4
Mean		8.74	75.5	6.78	1.012	662	7.9
B. Malignant Hypertension							
1	Ed.	23.7	26.8	2.8	1.0145	2000+	1.1
2	Gr.	23.0	19.1	1.7		435	94.5
3	La.		21.2	0.2		930	1.1
4	Ho.			1.7	1.014	267	20.4
5	McK.	26.1	35	4.4	1.015	280	26.6
6	Coo.	31.6	39.7	1.5	1.014	340	37.5
7	Ar.	26.1	36.5	1.7	1.014	275	2.3
8	Re.	17.5	25.6	3.8	1.012	380	8.0
9	Ch.		58.5	1.4	1.012	300	10.5
10	He.	17.6	35.7	1.5	1.011	350	4.3
Mean		23.65	33.1	2.07	1.013	605	20.6

Comparison of urea clearance, blood urea nitrogen concentration, maximum urinary non-protein specific gravity, proteinuria and sediment counts of red blood cells (R.B.C.) and casts in patients suffering from terminal glomerulonephritis and those suffering from malignant hypertension. The order of listing is the same as in tables 1 and 2. Where data were not available or were obtained at such a time that they are not comparable with data presented in the preceding tables, they are omitted.

tion is higher than the normal among the hypertensives, it is within the normal range among the nephritics. (4) Renal ischemia, evidenced by a diminished rate of effective renal blood flow per unit of tubular secretory tissue (normal  $23.86 \pm 3.93$  c.c. per minute, by calculation from Smith<sup>9</sup>) is present in nine of 10 malignant hypertensives, where the mean less twice standard deviation is taken as the lower limit of normal. Such an ischemia did not occur among the nephritics, whose values for this function were either normal, in the upper range of normal or, in one instance, about 400 per cent of normal. Comparison of the rates of effective renal blood flow with the corresponding levels of arterial pressure indicates that renal ischemia among hypertensives is due to increased renal resistance; otherwise their higher

levels of arterial pressure would have increased rather than decreased renal blood flow. (5) The anemia of terminal glomerulonephritis, as measured by hematocrit index, somewhat exceeds that of malignant hypertension with renal failure; none of the hypertensives showed a value equal to or less than the mean of 27 per cent found in the nephritics; four of the cases of glomerulonephritis yielded values less than this mean. (6) The hypoproteinemia of terminal glomerulonephritis and that often found in malignant hypertension in renal failure greatly alter the significance which may be attached to filtration fraction in these circumstances as compared with that attributed to this function in normal people. When allowance is made for this variable by the calculation of corrected filtration fraction ( $F_7$ ) or  $DP_0^{S=7}$ , filtration would, in theory, cease in three of seven nephritics at levels of plasma protein content osmotically less than the normal, here taken as 7 gm. per 100 c.c. In contrast, only one of the hypertensive group would, in theory, have ceased filtering at a normal level of plasma osmotic pressure. It can be calculated that the average rate of glomerular filtration in the group would, in this concept, have been reduced from its actual value of 22 only to about 10 c.c. per minute.

*II. Focal Tubular Saturation in Terminal Glomerulonephritis.* We have described under the section on evaluation of the methods the possible occurrence of a state in which certain tubular areas, themselves severely injured and surrounded by fibrous tissue, would become saturated with diodrast and thus fail further to secrete it at a time when the secretory capacity of areas less severely injured was not yet exceeded. Restated, the concept demands that evidence be obtained of decreased renal extraction of diodrast from blood at levels of secretory rate ( $T_D$ ) less than the maximum ( $T_{mD}$ ) and when the amount of diodrast brought to the kidney in the blood is also less than  $T_{mD}$ . Decrease in diodrast extraction would be signified, apart from direct measurement, by low levels of diodrast clearance (or apparent effective renal blood flow) and high levels of filtration fraction, both out of proportion to values observed in the same patient at lower plasma diodrast concentrations or found in other patients similarly diseased. In table 3 we present data from three patients of the nephritic group in whom one or both of these conditions are fulfilled at low plasma concentrations of diodrast and at levels of diodrast secretion ( $T_D$ ) equal to about one third or less of the maximum ( $T_{mD}$ ).

These observations were made incidentally during the proposed determination of plasma diodrast clearance in these patients. Direct titration of the actual inequality of tubular secretory activity by the methods of Smith<sup>9</sup> was not attempted, nor do the data permit its calculation, for in none of these was true maximum plasma diodrast clearance determinable. Nevertheless, the evidence indicates clearly the occurrence of Focal Tubular Saturation. Since these findings were made in terminal glomerulonephritis and have not been observed in any of our hypertensive patients, it seems

that the phenomenon of a wide inequality of tubular secretory activity may be one of the characteristics of advanced glomerulonephritis. In such patients no estimation of renal blood flow or filtration is possible by present methods.

*III. Differentiation by Generally Available Means: Data of table 3.* In table 3 we summarize observations of renal function based on urea clearance, blood urea nitrogen content, maximum urinary non-protein specific gravity, proteinuria and counts of the urinary sediment.

The difference between the two groups found in regard to glomerular filtration rate (inulin clearance) is repeated in the levels of urea clearance, the mean of which in terminal glomerulonephritics is less than half the mean rate in malignant hypertension with renal failure. None of the hypertensives showed a value equal to or less than the mean of 8.7 c.c. per cent of normal found in the nephritics. As would be expected from the lower level of urea clearance, blood urea nitrogen content is much higher among the nephritics. Another difference appears in the rate of proteinuria, which is more than twice as great in nephritics as compared to the hypertensives of our group. None of the hypertensives exhibited proteinuria equal or greater than the mean of nearly 7 gm. per 24 hours found in the nephritics; however, the overlapping lower values of some patients in both groups and the nearly normal rate (0.04 gm. per 24 hours) in one nephritic indicate that this measurement is not diagnostic in the lower ranges.

No differentiation could be made from the values of maximum urinary non-protein specific gravity, nor from the counts of red blood cells or of white and epithelial cells in urinary sediment, the latter determination not being included in the tabulation. The mean rate of cylindruria was significantly higher in the hypertensive groups, but the means of both groups were widely overlapped in certain cases.

## DISCUSSION

The arguments on which depend the interpretation of our data have been presented above in our "Evaluation of Methods." We need therefore here concern ourselves only with the clinical significance of the data and the problems they solve or suggest in clinical physiology.

Mansfield, Mallory and Ellis,<sup>29</sup> in a review of the differential diagnosis of Bright's disease, indicate that much confusion exists about the term "malignant hypertension," as did Page,<sup>30</sup> in an earlier study of this question. We use it in the sense defined by Keith, Wagener and Kernohan,<sup>30</sup> i.e., as a syndrome of severe hypertension of unknown origin, characterized by retinal hemorrhages, exudates and papilledema and progressing rapidly to a fatal outcome. The term, terminal glomerulonephritis, as we have used it requires no definition, at least, not as a clinical syndrome.<sup>22</sup> Stated in an older terminology, the demonstration proposed in this and the succeeding papers of this series is the distinction between patients who exhibit "albu-

minuric retinitis" and suffer from renal failure and who, at the time of observation, have not progressed to uremia. To make this distinction is not an academic problem of "deadhouse" interest, but, rather, clinically possible and important. Its importance, apart from etiological and functional connotations, lies in the time of survival of the patients in each group from the date at which observations were begun. This, in our malignant hypertensives, was 6.3 weeks and, in the glomerulonephritics, 6.4 + months, the plus sign (+) indicating that, at the time of writing, one terminal glomerulonephritic (No. 4, Wi.) is alive after 12 months.

The ability of the nephritic patient to tolerate severe renal injury and still survive for long periods as compared with malignant hypertensives whose renal function is, on the whole, much less affected, suggests that factors other than renal failure are the coöperating causes of death in malignant hypertension. These factors may be grouped together as expressions of a more severe arterial and arteriolar disease, as will be shown in the second paper of this series. This fact points to the advisability of dropping the term "malignant nephrosclerosis," with its connotation of a localized or primary lesion of the kidneys, even in patients such as our malignant hypertensives with renal failure to whom it would seem specially to apply. To retain it, one would have to justify the terminology of "coronarioarteriosclerosis, benign or malignant," and "cerebroarteriosclerosis, benign or malignant," in malignant hypertensives whose symptoms are respectively cardiac or cerebral in origin.

The significant means by which this distinction can be made by study of renal function are summarized in table 4. Taking the nine points there presented, diagnosis can be made cumulatively and by exclusion in all but one (No. 10) of the malignant hypertensives and in all but one (No. 2) of the glomerulonephritics. In both the exceptional patients, as we shall show in the studies which follow, the diagnosis can be established by studies other than renal.

The usefulness of each of these diagnostic criteria is indicated in table 4 by scoring their application to the two groups of patients studied. Among the generally available means of study, urea clearance and proteinuria are shown to be of positive value in the diagnosis of terminal glomerulonephritis. Of the methods of study which depend on the excretion of diodrast and inulin, the determinations of tubular secretory capacity, inulin clearance and effective renal blood flow per unit of residual secretory capacity are the most useful in glomerulonephritis; effective renal blood flow, corrected filtration fraction and observed filtration fraction have their application in the diagnosis of malignant hypertension with renal failure. The significance of focal tubular saturation in critical diagnosis, although included in the tabulation, remains to be demonstrated in a larger series.

In the classical monograph on Bright's disease<sup>12</sup> by Van Slyke and his co-workers of which this report represents in fact the reëxamination of a

segment, structural changes were the basis of their analysis of the functional concepts then introduced, notably that of clearance. Indeed, Addis and Oliver<sup>32</sup> have pointed out that no author, treating of this topic, has neglected to correlate the clinical and functional findings with the anatomical changes found at autopsy, nor do we propose to overlook this point of view in a subsequent study. However, because it is the point of this paper that the diagnosis can and should be established by functional means before autopsy, we can only note the general points of correlation. Among the glomerulo-

TABLE IV

Application of Tests of Renal Function as Means of Diagnosis in Terminal Glomerulonephritis and Malignant Hypertension with Renal Failure

No.	Test	Application	
		Terminal Glomerulonephritis	Malignant Hypertension with Renal Failure
1	Diodrast clearance	if less than 40 c.c. per min. (3)	must be more than 40 c.c. per min. (0)
2	Inulin clearance	if less than 12 c.c. per min. (6)	must be more than 12 c.c. per min. (0)
3	Urea clearance	if less than 10 c.c. per min. (5)	must be more than 10 per cent of normal (0)
4	Filtration fraction	if less than 0.15 c.c. per min. (1)	if more than 0.30 c.c. per min. (7)
5	Tubular secretory capacity (T <sub>mp</sub> )	if less than 4.0 mg. per min. (8)	must be more than 4.0 mg. per min. (0)
6	Effective renal blood flow (HD/T <sub>mp</sub> )	if more than 25 c.c. per min. (5)	if less than 18 c.c. per min. (9)
7	Difference P <sub>0</sub> <sup>5-7</sup>	if less than - 4 mm. Hg (5)	if more than 10 mm. Hg (8)
8	Focal tubular saturation	may be characteristic (3)	not observed as gross phenomenon (0)
9	Proteinuria	if more than 7.0 gm. per 24 hrs. (4)	must be less than 7.0 gm. per 24 hrs. (0)

Application of tests of renal function to differential diagnosis. The values stated as limiting the diagnoses vary slightly from the data of tables 1 and 2 in the direction of increasing their significance. Although diagnosis is in any case cumulative, it is probable when data fall into the category, "if less than . . ."; it is excluded when the values observed are less than indicated under the category, "if more than. . ." Diagnosis is made by concurrence of positive findings. The numerals bracketed in relation to each test under the two diseases studied indicate the frequency of the occurrence of each finding as a useful criterion of diagnosis.

nephritics our data indicate a more or less characteristic depression of the rate of glomerular filtration and of tubular secretory capacity as compared to patients suffering from malignant hypertension with renal failure. These characteristics of the nephritic accord with the smaller, and more fibrous kidneys with greater parenchymal loss and glomerular intra- and extra-capillary disease found in kidneys of such patients. The high values of observed filtration fraction in malignant hypertension, the presence of renal ischemia and severe hypertension, would seem to agree with the concept (Goldring, Ranges, Chasis and Smith<sup>17</sup>) that such patients have a great deal

of renal vasoconstriction, whose resistance more than counters the increase of arterial pressure and thus reduces renal blood flow, and that the locus of this constriction is principally in the glomerular efferent arterioles. That this is indeed the case has been difficult to reconcile with the hyperplastic and necrotizing changes of the afferent arterioles characteristic of patients with malignant hypertension. This paradox seems to us to be reconciled by our finding that values of corrected filtration fraction are very low in two cases of the group and within the normal range in four. In other words, in spite of the great increase of systemic arterial pressure, the hydrostatic pressure within the glomerular capillaries would have been insufficient to maintain a filtration from the glomerular plasma in one patient and barely so in another had the plasma protein content been normal, and, in another four, hydrostatic pressure was not abnormally increased. We and others have reviewed evidences which point to the uniform presence of efferent arteriolar constriction in arterial hypertension. We do not believe that it was absent in those patients whose levels of corrected filtration fraction do not point to its presence, but rather, we suggest that the degree of afferent arteriolar sclerosis had in these been so great as to reduce intraglomerular hydrostatic pressure to normal or subnormal levels in spite of the separate activities of systemic hypertension and efferent constriction which tend to raise it. The functional data are thus shown to be altogether consistent with anatomical findings. Even the demonstration of focal tubular saturation in cases of glomerulonephritis, with its suggestion of the presence of nephrons largely deficient in secretory capacity, and removed from other healthier or hyperplastic nephrons by boundaries of fibrous tissue through which interstitial fluid does not move rapidly, is altogether consistent with the anatomical pattern of this disease, as demonstrated by Oliver.<sup>33</sup> This inequality of tubular activity, although to be expected in minor degree in malignant hypertension with renal failure, would not be as characteristic of a disease in which the death of nephrons presumably follows rapidly on the obstruction of afferent arterioles, rather than slowly as glomerular capillaries are thickened, while still canalized and eventually obliterated. The high levels of apparent renal blood flow per unit of residual tubular tissue found in glomerulonephritis may also be consistent with the glomerular, rather than pre-glomerular character of the disease. A high rate of blood flow through residual tubular tissue might well follow the slow obliteration of glomeruli, with the possibility of formation of pre-glomerular afferent arteriolar shunts (Ludwig's arteriole) of lower vascular resistance than the combined resistances of constricted afferent and efferent arterioles, whereas, because of low hydrostatic pressure, such shunts would have little stimulus to open in the course of necrotizing and hyperplastic afferent arterioles. Alternatively, the apparent high rate of tubular perfusion in glomerulonephritis may well be a reflection of "vicarious clearance," i.e., excretion of diodrast by intact or hyperplastic tubules when it cannot be excreted by adjacent tubules



deficient in secretion. In any case, the reconciliation of functional and structural findings in the aspects of Bright's disease with which we here deal seems to us to have been made.

Since it is the subject of a separate communication, we shall here only note in passing that the values of corrected filtration fraction observed in four of the glomerulonephritics and one of the patients with malignant hypertension indicate that, with similar setting of blood pressure and arterioles, glomerular filtration would either have ceased or have been almost absent, had these patients not also been hypoproteinemic. As regards the state of the vascular system and the possibility of its being adjusted to maintain filtration had plasma proteins been normal, we note that hypertension was present and severe in both groups, that it is very likely that the glomerular efferent arterioles were constricted in these patients also, and that the afferent arterioles were also arteriolosclerotic in both, so that adjustment to increase filtration by increasing pressure, constricting efferent or dilating afferent would have been difficult or impossible. Hypoproteinemia was, therefore, life-saving in the patients in whom it was present. We are thus led to the view that hypoproteinemia in renal disease is teleologically homeostatic, and that the stimulus which provokes it is a relative deficiency of glomerular filtrate in the residually intact tubular tissue.

#### SUMMARY

The distinction between patients who show renal failure which has not progressed to uremia and is due respectively to terminal glomerulonephritis and malignant hypertension, is difficult. Because it is left for the pathologist to make the differentiation, the concept has grown that it is not clinically possible to establish it by study of renal function. That this is not the case we have shown by studies based on the excretions of diodrast and inulin, or urea and urinary protein, on the concentrating power of the kidneys, the urinary sediment, arterial pressure, hematocrit index and serum protein content. The studies were done in 10 patients from each group, selected because they presented the lowest levels of renal function observed in each series in the absence of the clinical syndrome of uremia.

Terminal glomerulonephritis is distinguished by a low rate of glomerular filtration, of tubular secretory capacity, and, usually, a higher rate of proteinuria than appear in malignant hypertension with renal failure. In spite of the lower level of renal excretory function in terminal glomerulonephritis, such patients survive more than four times as long as do patients with malignant hypertension in renal failure. The changes of renal function usually demonstrable in the terminal nephritic are in accord with the structural changes in the kidneys of such patients, in that they indicate lesions glomerular and capillary in locus, associated with great parenchymal destruction and fibrous replacement and suggest the frequent occurrence of large inequalities of function in the remaining nephrons.

In malignant hypertensives with renal failure, intraglomerular hydrostatic pressure seems often to be increased above the normal and the flow of blood through the residue of intact tubular tissue is diminished, the latter presumably as the result of arteriolar constriction and (afferent) arteriolar sclerosis. A subsequent communication in this series will establish the co-operation of severe arteriolar and arterial disease with renal failure as the cause of death in patients of this group. In some of these patients, in spite of greatly increased arterial pressure and presumptive constriction of glomerular efferent arterioles, intraglomerular hydrostatic pressure seems not to be increased above the normal or is even low. This observation testifies to the severity of afferent arteriolar sclerosis or constriction in these patients. The conclusion is drawn that in these, as in the terminal glomerulonephritics, the implications of functional study agree with what is known of the structural changes caused by the disease.

Evidence is obtained which suggests that the hypoproteinemia of Bright's disease, whether it occurs during chronic glomerulonephritis or in malignant hypertension with renal failure, apparently serves as a means of maintaining glomerular filtration when, in the absence of hypoproteinemia, the proportion of water filtered through the glomeruli would be grossly deficient or nil.

The authors wish to acknowledge the skillful assistance given in these studies by Truman Woodmansee, B.S., Mrs. E. Bowers Alward, R.N., and Miss Lucile Clary, R.N., associates in the Lilly Laboratory for Clinical Research.

#### BIBLIOGRAPHY

1. Original Papers of RICHARD BRIGHT on Renal Disease. OSMAN, A. A., 1937. Oxford University Press, London. Humphrey Milford. 1937.
2. SMITH, H. W., GOLDRING, W., and CHASIS, H.: The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney, *Jr. Clin. Invest.*, 1938, xvii, 263.
3. CORCORAN, A. C., and PAGE, I. H.: Applications of diphenylamine in the determination of levulose in biological mediums. I. The determination of inulin, *Jr. Biol. Chem.*, 1939, cxxvii, 601.
4. CORCORAN, A. C., and PAGE, I. H.: The determination of diodrast-iodine in blood and urine, *Jr. Lab. and Clin. Med.*, 1943, xxviii, 1514.
5. SMITH, H. W.: *The physiology of the kidney*, 1937, Oxford University Press, New York.
6. SMITH, W. W., and SMITH, H. W.: Protein-binding of phenol red, diodrast and other substances in plasma, *Jr. Biol. Chem.*, 1938, cxxiv, 107.
7. WHITE, H. L., and HEINBECKER, P.: Observations on inulin and diodrast clearances and on renal plasma flow in normal and hypophysectomized dogs, *Am. Jr. Physiol.*, 1940, cxxx, 454.
8. CORCORAN, A. C., SMITH, H. W., and PAGE, I. H.: The removal of diodrast from blood by the dog's explanted kidney, *Am. Jr. Physiol.*, 1941, cxxxiv, 333.
9. SMITH, H. W.: *Lectures on the kidney*, 1943, University Extension Division, University of Kansas, Lawrence.
10. CORCORAN, A. C., and PAGE, I. H.: Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs, *Jr. Exper. Med.*, 1943, lxxviii, 205.

11. CORCORAN, A. C., and PAGE, I. H.: Renal blood flow in experimental renal hypertension, *Am. Jr. Physiol.*, 1942, cxxxv, 361.
12. FOUTS, P. J., CORCORAN, A. C., and PAGE, I. H.: *Am. Jr. Med. Sci.*, 1941, cci, 313.
13. BOBEY, M. E., LONGLEY, L. P., DICKES, R., PRICE, J. W., and HAYMAN, J. M., JR.: The effect of uranium poisoning on plasma diodrast clearance and renal plasma flow in the dog, *Am. Jr. Physiol.*, 1943, cxxxix, 155.
14. NICHOLSON, T. F., URQUHART, R. W. T., and SELBY, D. L.: Renal function as affected by experimental unilateral kidney lesions. I. Nephrosis due to sodium tartrate, *Jr. Exper. Med.*, 1938, lxxviii, 439.
15. FINDLEY, T., EDWARDS, J. C., CLINTON, E., and WHITE, H. L.: Clearance of diodrast, phenolphthalein and inulin in hypertension and in nephritis, *Arch. Int. Med.*, 1942, lxx, 935.
16. SMITH, H. W.: Note on the interpretation of clearance methods in the diseased kidney, *Jr. Clin. Invest.*, 1941, xx, 631.
17. GOLDRING, W., CHASIS, H., RANGES, H. A., and SMITH, H. W.: Effective renal blood flow in subjects with essential hypertension, *Jr. Clin. Invest.*, 1941, xx, 631.
18. CORCORAN, A. C., TAYLOR, R. D., and PAGE, I. H.: Acute toxic nephrosis, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 81.
19. GOLDRING, W., CHASIS, H., RANGES, H. A., BRADLEY, J. E., and SMITH, H. W.: The application of saturation methods to the study of glomerular and tubular function in the human kidneys, *Jr. Mt. Sinai Hosp.*, 1943, x, 59.
20. LAMPORT, H.: Formulae for afferent and efferent arteriolar resistance in the human kidney: an application to the effects of spinal anesthesia, *Jr. Clin. Invest.*, 1941, xx, 535.
21. LAMPORT, H.: Improvements in calculation of renal resistance to blood flow. Charts for osmotic pressure and viscosity of blood, *Jr. Clin. Invest.*, 1943, xxii, 461.
22. VAN SLYKE, D. D., STILLMAN, E., MOLLER, E., EHRLICH, W., MCINTOSH, J. F., LEITER, L., MACKAY, E. M., HANNON, R. R., MOORE, M., and JOHNSTON, C.: Observations on the courses of the different types of Bright's disease and on the resultant changes in renal anatomy, *Medicine*, 1930, ix, 257.
23. CHASIS, H., and SMITH, H. W.: The excretion of urea in normal man and in subjects with glomerulonephritis, *Jr. Clin. Invest.*, 1938, xvii, 347.
24. ADDIS, T., and SHEVKY, E.: A test of the capacity of the kidney to produce urine of high specific gravity, *Arch. Int. Med.*, 1922, xxx, 559.
25. ALVING, A. S., and VAN SLYKE, D. D.: The significance of concentration and dilution tests in Bright's disease, *Jr. Clin. Invest.*, 1934, xiii, 969.
26. CORCORAN, A. C., and PAGE, I. H.: Quantitative formulation of maximum urinary specific gravity, *Jr. Mt. Sinai Hosp.*, 1942, viii, 459.
27. HAYMAN, J. M., JR., MARTIN, J. W. JR., and MILLER, M.: Renal function and the number of glomeruli in the human kidney, *Arch. Int. Med.*, 1939, lxiv, 69.
28. NEWBURGH, J. D.: The changes which alter renal osmotic work, *Jr. Clin. Invest.*, 1943, xxii, 439.
29. MANSFIELD, J. S., MALLORY, G. K., and ELLIS, L. B.: The differential diagnosis of chronic Bright's disease, *New England Jr. Med.*, 1943, ccxxix, 387.
30. KEITH, N. W., WAGENER, H. P., and KERNOHAN, J. W.: Syndrome of malignant hypertension, *Arch. Int. Med.*, 1928, xli, 141.
31. PAGE, I. H.: A clinical study of malignant hypertension, *Ann. Int. Med.*, 1939, xii, 978.
32. ADDIS, T., and OLIVER, J.: The renal lesion in Bright's disease, 1931, Paul B. Hoeber, New York.
33. OLIVER, J.: Architecture of the kidney in chronic Bright's disease, 1939, Paul B. Hoeber, New York.

# DIFFERENTIAL DIAGNOSIS OF TERMINAL GLOMERULONEPHRITIS AND MALIGNANT HYPERTENSION. II. CARDIAC ASPECTS\*

By R. D. TAYLOR, M.D., K. G. KOHLSTAEDT, M.D., A. B. RICHTER, M.D.,  
F.A.C.P., and IRVINE H. PAGE, M.D., F.A.C.P.,  
*Indianapolis, Indiana*

This communication is concerned with the results of study of the heart and to a lesser extent the circulation in the same two groups of patients considered in the companion paper (Corcoran and Page<sup>1</sup>) with the aim of achieving the differential diagnosis. It is worth reemphasizing that the clinical pictures resulting from terminal Bright's disease and terminal malignant hypertension with renal failure are very similar. From these similarities and their differences in courses arises the need for objective and accurate methods of differential diagnosis.

There have been numerous studies<sup>2, 3, 4, 5, 6, 7, 8, 9</sup> of the heart in malignant hypertension, and fewer<sup>9, 10</sup> in terminal glomerulonephritis. However, detailed comparison of the heart in the two morbid conditions appears not to have been made though some of its aspects have been reviewed (Page<sup>10</sup>). From the point of view of differential diagnosis, this is really the nub of the matter and is the object of this paper.

## METHODS

Ten patients with malignant hypertension and 10 with chronic glomerulonephritis were chosen from the records of the Lilly Clinic. These cases are the same as those in communication I and are identified by the first two letters of each patient's name. They were selected because of clinical similarity and represent the stage of both diseases when uremia was imminent.

Pertinent findings in each history and physical examination were selected. Venous pressure was measured in centimeters of blood rising into a tube containing citrate, connected to a No. 19 needle in an antecubital vein. Circulation time from arm to lung and arm to tongue was determined by injecting magnesium sulfate and ether intravenously. Vital capacity was determined in per cent of normal by means of the McKesson-Scott vital capacity apparatus (McKesson Appliance Co., Toledo, Ohio).

Deviation of the heart from predicted normal size was computed from two meter chest films according to the method of Ungerleider and Clark.<sup>11</sup> Electrocardiograms always included the conventional limb leads and one precordial lead, CFIV, and in some cases six chest leads, V<sub>1</sub> to V<sub>6</sub>. Ballistocardiographic tracings were taken as described elsewhere.<sup>12</sup> Stroke volume,

\* Received for publication February 3, 1944.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Indiana.

and cardiac output were computed from these using the area method of Starr, Rawson, Schroeder and Joseph.<sup>13</sup> Peripheral resistance was calculated from Bazzett, Cotton, and Laplace's formula,  $P.R. = 3PM/CI$ , (Normal 80 to 120)<sup>14</sup> where  $P.R.$  = peripheral resistance,  $P.M.$  = mean arterial pressure (arbitrarily, diastolic pressure + one-half of pulse pressure) and  $C.I.$  = cardiac output in liters per minute per square meter of body surface.

## RESULTS

*1. History and Physical Findings.* The average duration of disease in malignant hypertensives from the first symptom or sign to the present observation was five years, and in chronic nephritis 11 years (table 1). All patients with malignant hypertension complained of some degree of dyspnea of cardiac origin and in spite of the comparative brevity of the disease, five of them developed congestive heart failure. Four of 10 malignant hypertensives complained of paroxysmal nocturnal dyspnea. The physical findings of pulmonary edema, hepatic enlargement, and dependent edema substantiated the cardiac origin of the symptoms in each case. Gallop rhythm was recorded in four of the five patients with heart failure.

In sharp contrast to this picture of cardiac failure (Grades I to IV)\* developing within five years in the malignant hypertensives only one case (Grade I) occurred in the nephritic group during the course of 11 years. This patient developed congestive heart failure 33 years after onset of renal disease. Five of the ten nephritics complained of some degree of dyspnea, and edema was noted in seven. However, the absence of physical and laboratory findings of heart failure suggested other causes for these complaints. Such cause might well be the well known anemia, hypoproteinemia, and acidosis of chronic nephritis.

*2. Venous Pressure, Vital Capacity, and Circulation Time.* The studies of venous pressure, vital capacity, and circulation time in themselves did not differentiate the circulatory status of the two groups but merely confirmed the other findings. The venous pressure was higher, the vital capacity was lower and the circulation time was longer in the malignant hypertensives (table 1).

*3. Teleroentgenograms.* The degree of cardiac enlargement in the two groups was almost identical (table 2) (hypertensives + 22 per cent, range 0 to 50 per cent; nephritics + 23 per cent, range — 2.5 to 50 per cent). This equality assumes significance in light of the duration of each disease, since it suggests that malignant hypertension produces cardiac enlargement at more than twice the rate of chronic glomerulonephritis. However, the characters of the cardiac silhouettes in the two groups were quite different. Among the malignant hypertensives the shadows were bootshaped and indicated marked left ventricular enlargement. This group also showed tor-

\* American Heart Association.



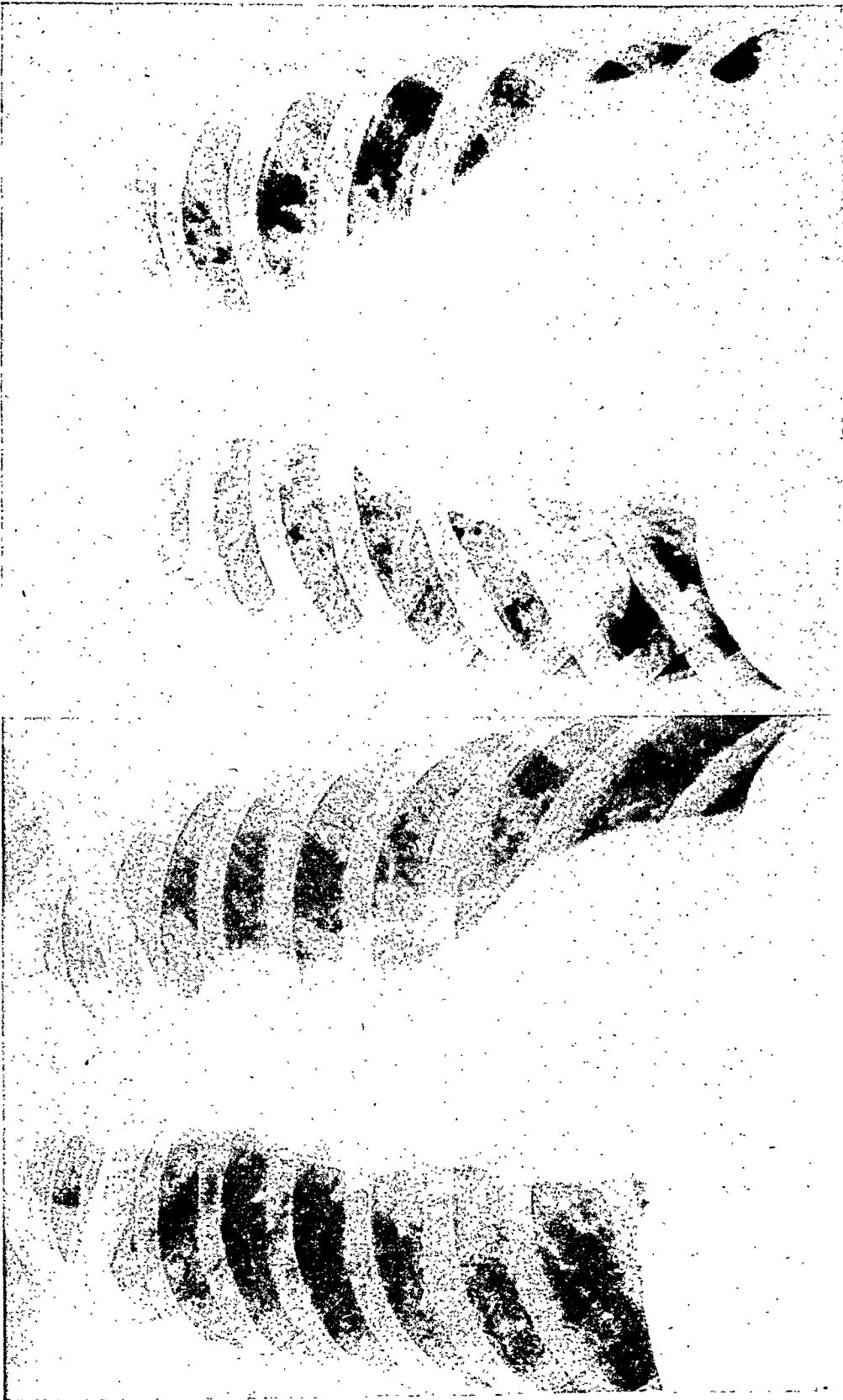


FIG. 1 (A)

FIG. 1 (B)

TABLE II

Summary of Electrocardiographic and Teleroentgenological Findings

Methods of estimation of cardiac size is explained in the text. R and S refer to these waves in the respective leads of the electrocardiogram. PC includes all precordial leads of the electrocardiogram.

of the electrocardiogram.																	
Case	Pulse Rate	Receiving Digitalis	Per Cent of Cardiac Enlarge-ment	Potential in Millivolts					Depressed ST Segment Lead				T Waves Inverted Lead				Interpre-tation
				R <sub>1</sub>	R <sub>2</sub>	S <sub>2</sub>	S <sub>3</sub>	R <sub>1</sub> +S <sub>3</sub>	1	2	3	PC	1	2	3	PC	
Malignant Hypertensives																	
RE	75	Yes	20	11	14			11					*	*	*		Normal
CO	100	Yes	10	7	14			7									Abnormal
HI	85	No	10	8	17			8	*	*		*					Abnormal
AR	90	No	20	6	18			6	*	*		*	*				Abnormal
HO	90	Yes	33	6	10		4	10				*	*	*			Abnormal
LA	120	Yes	50	7	8	25	7	14					*	*			Abnormal
CH	90	No	35	11	14		4	15	*	*	*	*	*	*		*	Abnormal
GR	85	Yes	23	11	13		5	16					*	*		*	Abnormal
Mc	105	No	29	18	18			18	*	*			*	*			Abnormal
ED	100	Yes	0	22	15	8	16	38					*	*		*	Abnormal
Nephritics																	
HI	85	No	20	10	15			10									Normal
FR	65	No	43	3	7			3									Normal
HA	88	No	32	4	8			4									Normal
WI	80	No	-2.5	7	7			7									Normal
FI	76	No	28	8	10			8									Normal
CO	70	No	22	15	14			15					*	*			Abnormal
HU	65	No	50	8	4	3	6	14									Abnormal
MI	115	No	10	13	13		10	23									Abnormal
WE	80	Yes	10	10	8		4	14					*	*			Abnormal
SM	90	No	25	9	7		5	4									Abnormal

tuosity and elongation of the aorta. One nephritic showed the same picture. The remaining nine nephritics showed generalized enlargement with globular shadows suggesting dilatation with no striking changes in the aortas (figure 1).

4. *Electrocardiographic Studies.* The electrocardiogram was found to aid in differentiating the two groups by pointing to greater myocardial damage among the malignant hypertensives (table 2). In this group only one patient showed an electrocardiographic pattern that was normal, whereas five such tracings were found among the nephritics. The abnormalities in both groups consisted of left axis deviation, inversion of T waves and depression of the ST segments. These last two changes were predominantly present

A. MC. Malignant hypertension. This cardiac shadow deviates 29 per cent from the predicted normal. It represents the typical left ventricular enlargement and aortic elongation and tortuosity of malignant hypertension.

B. FR. Chronic glomerulonephritis. This silhouette deviates 43 per cent from the predicted normal. It represents generalized cardiac enlargement suggesting dilatation seen in chronic nephritis. The aorta is not appreciably enlarged.



in the standard Leads I and II and occurred in nine malignant hypertensives and two nephritics. Only two tracings showed changes in Lead III and six showed ST segment or T wave changes in Leads  $V_5$  and  $V_6$ . Pericarditis was not present in either group while these observations were being made.

5. *Ballistocardiographic Studies.* The clinical use of the ballistocardiograph since Henderson's original experiments<sup>15</sup> has been developed by Starr

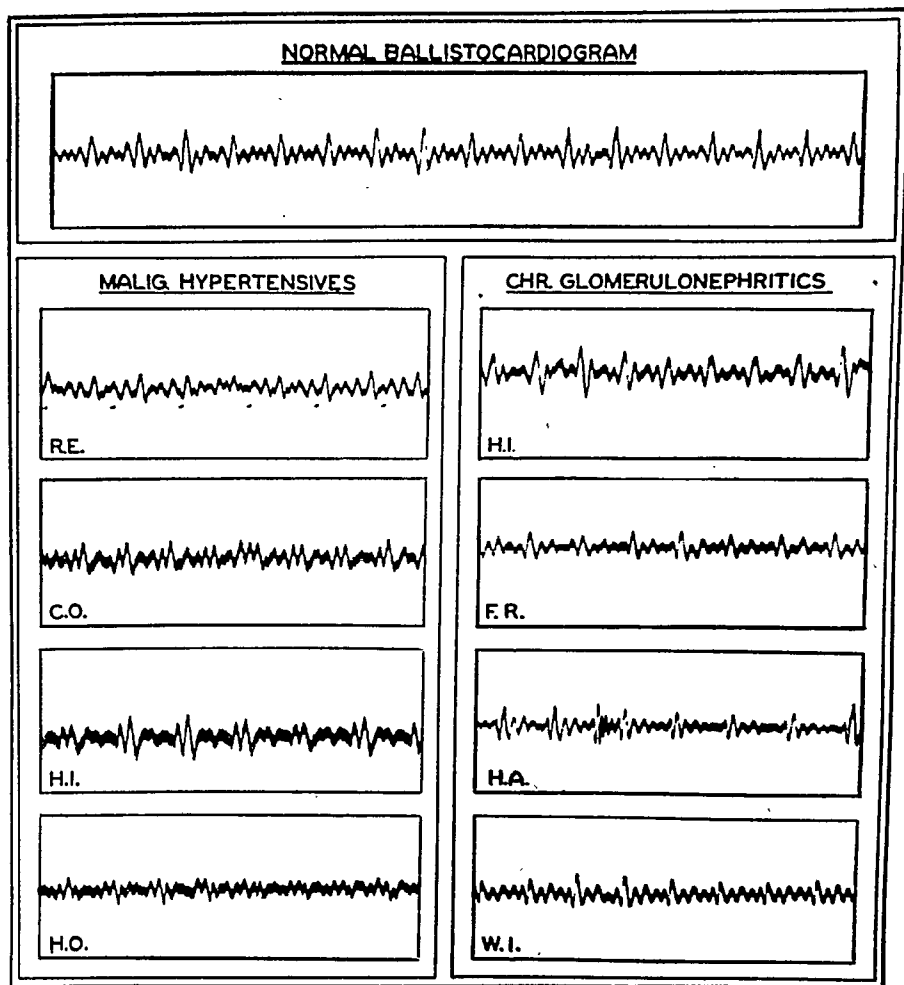


FIG. 2. Ballistocardiograms of malignant hypertensives and chronic glomerulonephritics. The tracings of the hypertensives are bizarre whereas those of the nephritics with the same degree of cardiac enlargement and almost the same arterial pressure (172 mm. Hg and 152 mm. Hg average mean arterial pressure) are almost normal.

and Schroeder.<sup>16</sup> The apparatus consists of a suspended bed with free longitudinal motion. The force of the blood ejected by the heart against the aortic arch and the pulmonary artery sets up ballistic impulses in the body which are transmitted to the bed and so recorded on a moving film. When the heart, great vessels and circulation are normal, a characteristic and consistently reproducible series of waves are recorded during each cardiac cycle (figure 2).

The amplitude of the first negative and positive waves express the volume of blood ejected with each heart beat. For this relationship, Starr<sup>13</sup> has computed formulae which permit the estimation of cardiac output in cubic centimeters per beat. Since pulse rate is also recorded, minute volume output of the heart can be calculated. Cournand, Ranges and Riley<sup>17</sup> compared the accuracy of these results with those attained by the direct Fick method. They were consistently lower, indicating the necessity of increas-

TABLE III

Stroke Volume, Cardiac Index, Peripheral Resistance and Ballistocardiograms

Stroke volume, cardiac index and peripheral resistance were calculated from the ballistocardiogram and mean arterial pressure. The methods are explained in the text.

Patient	Mean Arterial Pressure, mm. Hg. Diastolic and $\frac{1}{2}$ Pulse Pressure	Stroke Volume c.c.	Cardiac Index L./Min./1.73 Sq. M.	Peripheral Resistance P.R. = $\frac{3MP}{C.I.}$	Ballistic Tracing
Malignant Hypertensives					
RE	203	57	2.49	244	Bizarre
CO	173	50	2.58	201	Bizarre
HI	194	33	1.91	304	Bizarre
AR	149	41	2.13	210	Bizarre
HO	169	53	3.00	169	Bizarre
LA	165	61	2.64	188	Bizarre
GR	165	45	1.80	275	Bizarre
ED	159	44	2.13	224	Bizarre
Ave.	172	48	2.34	227	
Nephritics					
HI	149	65	3.67	122	Normal
FR	124	58	2.41	154	Slightly abnormal
HA	155	47	2.49	187	Normal
WI	145	51	2.39	182	Normal
CO	150	51	1.90	237	Normal
HU	141	77	2.93	144	Normal
MI	201	37	1.86	324	Slightly abnormal
WE	155	46	2.49	187	Bizarre
Ave.	152	54	2.52	192	

ing the final value for stroke volume by 18.5 per cent. This correction was made in our data.

Eight patients in each group were studied in this way.

a. *Characteristics of Ballistocardiographic Tracings.* All of the malignant hypertensives had ballistic tracings that were bizarre (table 3). By this we mean the waves were so distorted in their relationship one to the other and to the base line as to be completely unlike the normal pattern (figure 2). On the other hand, the nephritics' ballistocardiograms were in

most (five of eight) cases normal, and the abnormalities that were present were not sufficient to obscure the normal pattern except in the one who had developed congestive heart failure. Simple inspection of the ballistic patterns thus aided in the differentiation of the two diseases in 15 of the 16 cases studied.

*b. Blood Pressure, Stroke Volume, Cardiac Output, and Peripheral Resistance.* These hemodynamic studies had little significance either as individual tests or in individual cases, but taken collectively they showed a definite trend (table 3).

The average mean arterial blood pressure of the malignant hypertensives was higher than that of the nephritics (172 mm. Hg as compared to 152 mm. Hg), and the average stroke volume and cardiac output were smaller (48 c.c. and 2.34 L./min./sq. M. of body surface as compared to 54 c.c. and 2.52 L.). Since peripheral resistance is calculated from these values, that of malignant hypertension must be greater than that of chronic nephritis (227 as compared to 192). This difference of 18 per cent is not great in light of the normal variation of 80 to 120. This wide range of normal is due to the variation of normal arterial pressure while normal cardiac output is usually a constant function. In contrast, arterial pressure was greatly and consistently elevated in all our patients, and cardiac output was depressed in many. The variability of peripheral resistance found in normal people may not apply to such abnormal circumstances. We incline, therefore, to the view that peripheral resistance or sclerosis or both is greater in malignant hypertension than in chronic nephritis.

#### DISCUSSION

The preceding paper presented groups of 10 clinically similar cases of malignant hypertension and of chronic glomerulonephritis, and showed how differentiation may be made by studies of renal function. In this report we have analysed the cardiac and circulatory functions of these same patients with the hope of further aiding the differentiation.

It was pointed out in the first paper that nephritic patients can survive, and with suitable care in comparative comfort, with much less functioning renal tissue than can patients with malignant hypertension. It was concluded that factors other than renal failure were probably responsible for disability and death in the malignant hypertensives. The data presented here substantiate this by demonstrating a more severe and rapidly progressive disease of the heart and blood vessels in malignant hypertension. Cardiac and renal failure, therefore, are joint factors in the mortality of malignant hypertension.

The cardiac enlargement demonstrated by roentgenogram as being present in equal degrees in the two groups could have resulted from either hypertrophy or dilatation. The extent to which each of these mechanisms participated is not certainly known. However, as we have seen, the uniform

enlargement of heart and aorta in the nephritics suggests in them a preponderance of dilatation over hypertrophy (Fishberg<sup>18</sup>). The reverse is true in the malignant hypertensives whose enlargement was largely that of the left ventricle and whose aortas were both elongated and tortuous. Thus it seems likely that the equality of cardiac enlargement in the two groups was achieved by somewhat different mechanisms.

The greater degree of hypertrophy in the malignant hypertensives may be explained on two bases: (a) As an adaptation to a greater peripheral resistance, and (b) on less certain grounds, as an expression of greater coronary arterial and arteriolar sclerosis or constriction or both. This first suggestion is based on the observation of greater peripheral resistance and vascular disease in malignant hypertensives, the latter on the demonstration by Dauber and Katz<sup>19</sup> of ventricular hypertrophy in cholesterol atherosclerosis of chicks. Since the heart's weight is an index of its hypertrophy, the justness of the view that hypertrophy is more common in malignant hypertension is borne out by the finding that the hearts of such patients weigh more than do those of chronic nephritics (MacMahon and Pratt<sup>8</sup>). The uniform character of cardiac enlargement in chronic nephritis, presumably the result of overall dilatation, is not easily explained.

The tortuous and elongated aortas seen in malignant hypertension could be due, in part, to the different ages of the two groups (average 32 years in nephritis and 46 years in malignant hypertension), since the aorta loses elasticity and increases in size with passing years. Thus, according to Ungerleider and Gruber<sup>20</sup> 14 years aging in these decades would result in an aortic diameter 0.47 cm. greater at age 46 than at age 32. An estimation of the internal diameter of the aorta at 32 and 46 years of age (Bazzett<sup>14</sup>) shows a difference of 0.83 cm. But this can not be the whole story, since three malignant hypertensives of 35 years and under showed the same aortic pattern as did the older hypertensives whereas three nephritics of 37, 49 and 50 years of age did not. It would seem more probable that the greater stress and strain and small vessel sclerosis of malignant hypertension result in more aortic injury than develops in nephritis.

The electrocardiographic changes usually associated with hypertensive heart disease are left axis deviation, depressed ST segments, and inverted T waves in the standard and precordial leads. These patterns have been variously called chronic left ventricular strain (Barnes and Whitten<sup>21</sup>), coronary insufficiency and hypertrophy (Master<sup>22</sup>), impaired conduction pathways (Katz<sup>23</sup>), left ventricular hypertrophy (Gruber and Ungerleider<sup>24</sup>) and coronary artery sclerosis (Levine<sup>25</sup>). Experimentally the Robbs<sup>26</sup> have produced left axis deviation by dissecting away the exposed left ventricle of the dog and T wave changes by stretching the muscle fibers of the dog's left ventricle.<sup>27</sup> Hoff, Nahum and Kisch<sup>28</sup> have produced similar changes in the dog by applying cold and potassium chloride to the exposed ventricle. Certainly one or a combination of two or more of these clinical and ex-

perimental mechanisms must play a part in the production of the electrocardiogram characteristic of hypertensive heart disease.

In our cases the incidence of left axis deviation, T wave and ST segment changes was 3 to 1 in favor of malignant hypertension. In 10 malignant hypertensives there was only one normal tracing, whereas five were found among the nephritics. This frequency of normal electrocardiograms in chronic nephritis was formerly noted by Richter and O'Hare.<sup>10</sup> Consideration of the electrocardiographic findings can leave little doubt that the myocardial damage of malignant hypertension is more severe than that of chronic glomerulonephritis. Therefore, given a patient with findings common to both diseases and a normal electrocardiogram, the weight of evidence is in favor of chronic glomerulonephritis.

The most definitive differentiation of the cardiac status in these two conditions was furnished by simple inspection of the ballistocardiograms. Starr and Schroeder<sup>10</sup> were struck by the frequency of normal ballistic forms in the presence of gross cardiac abnormalities, emphasizing the adaptability of the heart muscle to disease. In the nephritic group, this compensatory mechanism made for almost normal tracings in all but one patient whereas those of the hypertensives were all bizarre. These data indicate that the heart of the malignant hypertensive is unable to compensate for its disabilities as well as the nephritic's heart.

The mechanism of the production of these consistently bizarre patterns of malignant hypertension is not known. The pronounced aortic abnormalities seen in the teleroentgenograms may be important. As we have suggested, these aortas are less elastic than those of the chronic nephritics who had less elongation and tortuosity. Since the target of blood ejected from the left heart is the arch of the aorta, distortion of this surface and loss of its elasticity could contribute to the more abnormal ballistocardiograms of malignant hypertension. In addition, the swings of the ballistocardiograph are dependent upon the impact of blood against both the arch of the aorta and the curve of the pulmonary artery. The rapidly enlarging and abnormal left ventricle of malignant hypertension may throw its stream of blood with greater comparative force than the more normal right ventricle whose pulmonary vascular resistance, at least in hypertensive dogs (Katz<sup>29</sup>), is not increased. It may also inject it into the aorta at a different and abnormal angle. The combination of these two mechanisms, cardiac and aortic, would offer an adequate explanation for the great discrepancy in the ballistocardiograms produced by equally enlarged hearts against almost the same arterial pressure.

Taylor and Page<sup>12</sup> suggested that the cardiac output was related to mean arterial pressure and cardiac size, i.e., cardiac output was proportional to:

$$\frac{\text{Cardiac size in per cent of normal}}{\text{Mean arterial pressure}}$$

The malignant hypertensives with slightly higher arterial pressure and roughly the same sized hearts should

thus have smaller cardiac outputs. This was observed here. It is a reflection of greater peripheral resistance in malignant hypertension which probably means more severe and more generalized arteriolar constriction or sclerosis or both.

The preceding paper presented evidence that factors other than renal failure were probably responsible for the fulminant course and early death of malignant hypertensives as compared to chronic nephritics. More severe heart disease and more generalized blood vessel disease in malignant hypertension seemed to be plausible explanation for this difference. The present study substantiates that view and therefore offers a useful diagnostic aid and means of offering prognosis in those stages of malignant hypertension and chronic glomerulonephritis which are superficially so alike. The significance of this assumes more than academic importance in view of the distinct survival periods of each group. The average survival period was one month among the malignant hypertensives and eight months or more among the chronic nephritics.

The diagnosis, when it is in question, may usually be made by evaluation of the cardiac change in terms of clinical signs and symptoms, of roentgenographic shadows, of electrocardiographic abnormalities, by the degree of increased peripheral resistance, and especially by the character of the ballistocardiographic pattern.

#### SUMMARY

1. The cardiac status of 10 patients with malignant hypertension in whom uremia was imminent was compared to that of 10 clinically similar chronic glomerulonephritics.

2. Five of 10 malignant hypertensive patients developed clinical signs of heart failure in an average disease duration of five years, whereas only one nephritic developed congestive failure in a group average of 11 years.

3. In these two periods the same degree of cardiac enlargement developed in both groups. In malignant hypertension the enlargement was primarily left ventricular and the aortas were long and tortuous. In nephritis the enlargement was globular and suggested dilatation.

4. Electrocardiographic evidence of hypertensive heart disease is usual in malignant hypertension and rare in chronic nephritis.

5. All of the malignant hypertensives had bizarre ballistocardiograms. This abnormality occurred in only one nephritic in whom it was associated with heart failure.

6. The blood pressure of malignant hypertension is usually higher, cardiac output is lower and peripheral resistance is greater, indicating more severe peripheral vasoconstriction or sclerosis or both as compared to chronic glomerulonephritis.

7. The differential diagnosis between terminal malignant hypertension and terminal glomerulonephritis can be made by detailed study of the heart

and circulation. Evidences of advanced heart disease are usual in malignant hypertension, whereas they are often indistinct or absent in nephritis.

## BIBLIOGRAPHY

1. CORCORAN, A. C., and PAGE, I. H.: Differential diagnosis of terminal glomerulonephritis and malignant hypertension. I. Renal aspects, *Ann. Int. Med.*, 1944, xxi, 747-764.
2. KEITH, N. M., WAGENER, H. P., and KERNOHAN, J. W.: Syndrome of malignant hypertension, *Arch. Int. Med.*, 1928, xli, 141.
3. MACMAHON, H. E., and PRATT, J. H.: Malignant nephrosclerosis, *Am. Jr. Med. Sci.*, 1935, cxcix, 221.
4. ELLIS, A.: Malignant hypertension (Schorstein Lecture), *Lancet*, 1938, 1, 977.
5. GOULEY, B. A.: Myocardial degeneration associated with uremiā in advanced hypertensive disease and chronic glomerular nephritis, *Am. Jr. Med. Sci.*, 1940, cc, 39.
6. SHELburne, S., and HAWLEY, J. L.: Retinal arteriovenous nicking, relation to enlargement of heart in ambulatory patients with hypertension, *Arch. Int. Med.*, 1942, lxi, 213.
7. SOLOMON, C., ROBERTS, J., and LISA, J.: The heart in uremia, *Am. Jr. Path.*, 1942, xviii, 729.
8. MARKHAM, J. D., and BLOOM, N.: Significance of electrocardiographic changes in malignant hypertension, *Jr. Lab. and Clin. Med.*, 1942, xxv, 1156.
9. PAGE, I. H.: A clinical study of malignant hypertension, *Ann. Int. Med.*, 1939, xii, 978.
10. RICHTER, A. B., and O'HARE, J. P.: The heart in chronic glomerular nephritis, *New England Jr. Med.*, 1936, ccxiv, 824.
11. UNGERLEIDER, H. E., and CLARK, C. P.: Study of transverse diameter of heart silhouette with prediction table based on teleoroentgenogram, *Am. Heart Jr.*, 1939, xvii, 92.
12. TAYLOR, R. D., and PAGE, I. H.: The effects of antipressor kidney extract, angiotonin, methyl guanidine and tyramine on cardiac output as measured by the ballistocardiograph in hypertensive and normal persons, *Am. Jr. Med. Sci.*, 1943, ccv, 66.
13. STARR, I., RAWSON, A. J., SCHROEDER, H. A., and JOSEPH, N. R.: Studies on the estimation of cardiac output in man, and of abnormalities in cardiac function, from the heart's recoil and the blood's impacts; the ballistocardiogram, *Am. Jr. Physiol.*, 1939, cxxvii, 1.
14. BAZZETT, H. C., COTTON, F. S., LAPLACE, L. B., and SCOTT, J. C.: The calculation of the cardiac output and effective peripheral resistance from blood pressure measurements with an appendix on the size of the aorta in man, *Am. Jr. Physiol.*, 1935, cxiii, 312.
15. HENDERSON, Y.: The mass-movements of the circulation as shown by a recoil curve, *Am. Jr. Physiol.*, 1905, xiv, 287.
16. STARR, I., and SCHROEDER, H. A.: Ballistocardiogram. II. Normal standards, abnormalities commonly found in diseases of the heart and circulation and their significance, *Jr. Clin. Invest.*, 1940, xix, 438.
17. Cournand, A., RANGES, H. A., and RILEY, R. L.: Comparison of results of the normal ballistocardiogram and a direct Fick method in measuring the cardiac output in man, *Jr. Clin. Invest.*, 1942, xxi, 287.
18. FISHBERG, ARTHUR M.: Hypertension and nephritis, 1940, Lea and Febiger, Philadelphia.
19. DAUBER, D. V., and KATZ, L. N.: Experimental cholesterol atheromatosis in omnivorous animal, the chick, *Arch. Path.*, 1942, xxxiv, 937.
20. UNGERLEIDER, H. E., and GRUBER, R.: Evaluation of heart size measurements, *Am. Heart Jr.*, 1942, xxiv, 494.
21. BARNES, A. R., and WHITTEN, M. B.: Study of T wave negativity in predominant ventricular strain, *Am. Heart Jr.*, 1929, v, 14.
22. MASTER, A. M.: Characteristic electrocardiograms and roentgenograms in arterial hypertension, *Am. Heart Jr.*, 1930, v, 291.

23. KATZ, L. N.: *Electrocardiography*, 1941, Lea and Febiger, Philadelphia.
24. GRUBER, R., and UNGERLEIDER, H. E.: Electrocardiographic criteria of left ventricular hypertrophy, *Arch. Int. Med.*, 1943, lxxii, 196.
25. LEVINE, S. A.: *Clinical heart disease*, ed. ii, 1940, W. B. Saunders Company, Philadelphia.
26. ROBB, R. C., and ROBB, J. S.: Experimental bundle branch block after ablation of one or both ventricles, *Am. Jr. Med. Sci.*, 1942, cciv, 313.
27. ROBB, J. S., and ROBB, R. C.: Hypertension electrocardiograms experimentally produced and anatomically explained, *Am. Jr. Med. Sci.*, 1942, cciii, 625.
28. HOFF, H. E., NAHUM, L. H., and KIRSCH, B.: Influence of right and left ventricles on the electrocardiogram, *Am. Jr. Physiol.*, 1941, cxxxi, 687.
29. KATZ, L. N., and STEINITZ, F. S.: Pulmonary arterial pressure in experimental renal hypertension, *Am. Jr. Physiol.*, 1940, cxxviii, 433.



# RUPTURE OF THE HEART IN MYOCARDIAL INFARCTION. EXPERIENCE IN A LARGE GENERAL HOSPITAL \*

By SIDNEY FRIEDMAN, M.D., and PAUL D. WHITE, M.D., F.A.C.P.,  
*Boston, Massachusetts*

SPONTANEOUS rupture of the heart, although always a dramatic episode and recognized as a pathological curiosity since the Middle Ages, has a clinical significance that is not even yet adequately recognized. For this reason and especially because of the finding of a high incidence of cardiac rupture among psychotic patients with acute myocardial infarction reported in a companion paper in this journal,<sup>1</sup> it was thought wise to determine the frequency and circumstances of rupture of the heart in a large general hospital in the same part of the country and among persons of age and social status comparable to those of the psychotic cases.

Martland,<sup>2</sup> in 1940, in his rôle of medical examiner, reported finding rupture of the myocardium as a cause of death in 42 (2.1 per cent) of 2,000 cases of individuals who died suddenly; all of the 2,000 cases were over 10 years old, the majority between 40 and 65, five-sixths males and one-sixth females. In this same series coronary occlusion with thrombosis was present in 304 cases, coronary occlusion without thrombosis in 314 cases, "coronary insufficiency" in 112 cases, and aneurysm of the left ventricle in 59 cases.

Among 25,000 postmortem examinations at the Los Angeles County Hospital from 1924 to 1941 there were 865 cases of unhealed myocardial infarction, of which 72 (8 per cent) showed cardiac rupture.<sup>3</sup>

*Present Study.* Among 2,967 autopsies performed at the Massachusetts General Hospital, between March 1933 and November 1940, the protocols of 270 cases with myocardial infarction were found and analyzed. Of this number 105 had suffered recent myocardial infarction and the remaining 165 showed old coronary occlusion with healed infarction. In this latter group numerous ventricular aneurysms were found but not a single case of rupture occurred. Of the 105 cases of acute infarction, all occurring within two weeks of death, 10 had as the immediate cause of death a rupture of the ventricle with tamponade from hemopericardium.

## CASE REPORTS

*Case 1.* Protocol No. 6697 is that of an 80 year old male who was well until seven days before his death when he developed slight pain in his left axilla without fever or dyspnea. His blood pressure, which had been 160 mm. mercury systolic and 80 mm. diastolic, was found to be 110 mm. systolic and 70 mm. diastolic. The day fol-

\* Received for publication December 23, 1943.

From the Cardiac Laboratory of the Massachusetts General Hospital, Boston, Massachusetts.

TABLE I  
Summarizing the Data of Our Ten Cases of Cardiac Rupture

Age	Sex	Duration from Clinical Onset	Sedation	Previous Cardiac History	Pathological Findings
79	M	9 days	Adequate	Angina pectoris for 3 months. Hypertension of variable period	Heart enlarged. Occl. of d.b. of L.C.A.
66	M	2 days	Inadequate	None	Heart slightly enlarged. Occl. of d.b. of L.C.A. L.V. infarct and laceration
80	M	7 days	Adequate but not kept in bed because of uncertainty of diagnosis	Slight hypertension	Heart moderately enlarged. L.V. infarct and perforation. Occl. of d.b. of L.C.A.
64	F	12 hours	Inadequate because of violence, result of cerebral thrombosis	Angina pectoris for 5 years. Hypertension	Heart not enlarged. Occl. d.b. of L.C.A. Infarct of L. and R. ventricle
67	F	4 days	Inadequate because of violence due to cerebral thrombosis	Hypertension	Heart moderately enlarged. Occl. of circumflex branch of R.C.A. Infarction of posterior surface of L.V. with perforation
62	M	14 days	Adequate	Angina pectoris for 1 month	Occl. of d.b. of L.C.A. and circumflex branch of the right. Heart moderately enlarged. Infarction of L.V. with perforation
51	M	14 hours	Adequate		Heart slightly enlarged. Occl. of d.b. of L.C.A. Infarct and perforation of L.V.
55	M	12 hours	Adequate	Angina pectoris for 2½ wks.	Heart not enlarged. Occl. of d.b. of L.C.A. Infarct of L.V. with perforation
66	F	2 days	Inadequate	No history	D.B. of L.C.A. occl. Heart not enlarged. Infarct of left ventricle with laceration
67	M	4 days	Adequate	Angina pectoris for 2 months	Circumflex branch of L.C.A. occl. Infarct of left ventricle with laceration

L.V.—left ventricle.  
R.V.—right ventricle.  
L.C.A.—left coronary artery.

R.C.A.—right coronary artery.  
occl.—occlusion.  
d.b.—descending branch.

lowing this episode râles were found in his lung bases and an irregular pulse was noted. Five days later he was found to have slightly more congestion, and an electrocardiogram showed T waves consistent with acute coronary occlusion. He was found

dead in bed the following day. Postmortem examination revealed 350 c.c. of blood in the pericardial sac. The heart weight was 450 grams. An area of acute infarction of the left ventricle, 5 cm. in diameter, was found with a small perforation in the center. The descending branch of the left coronary artery was occluded by a fresh thrombus.

Comment: This man died quite suddenly when he appeared to be "getting better." He had been seen within a few minutes of his death and did not then appear very ill.

Case 2. Protocol No. 7116 is that of a 67 year old female, known to have diabetes and hypertension, who, four days after a cataract operation, developed diabetic acidosis which was treated vigorously. The next day she complained of pain in the left chest. A slight elevation of temperature and râles in both lung bases were found. Her temperature continued to rise and she became restless and disoriented and thrashed about to get out of bed; four days after the first onset of chest pain she developed hemiplegia, collapsed, and died. Postmortem examination revealed 900 c.c. of blood in the pericardial sac; heart weight 450 grams. There was a recent infarct of the posterior surface of the left ventricle with perforation through a soft saccular aneurysm. The circumflex branch of the right coronary artery was found to be occluded by a recent thrombus.

Comment: In this case violence may have contributed to the myocardial rupture.

Case 3. Protocol No. 7204 is that of a 64 year old female admitted to the hospital for symptoms of intestinal obstruction of two weeks' duration. She was known to have hypertension and diabetes, and she had suffered from angina pectoris for five years. While being examined she suddenly developed severe precordial hyperesthesia and apparent pain, thrashed about, collapsed, and died 12 hours after admission to the hospital. Postmortem examination revealed 250 c.c. of blood in the pericardial sac; the heart weight was 725 grams. There was a recent infarct of the left and right ventricles. All coronary vessels were markedly arteriosclerotic. There was a fresh thrombus in the descending branch of the left coronary artery. Recent infarcts were observed in the lenticular nuclei of the brain.

Comment: Violence, because of the patient's mental state, may have contributed to the final episode of myocardial rupture.

Case 4. Protocol No. 7485 is that of a 66 year old female who had a typical attack of coronary thrombosis two days prior to her death. Death was sudden and no further information was available. Postmortem examination revealed 200 c.c. of blood in the pericardial sac and a heart weight of 250 grams. Two lacerations were seen on the anterior aspect of the left ventricle in the center of the recently infarcted myocardium. The descending branch of the left coronary artery was occluded by a fresh thrombus.

Comment: No apparent physical strain was to be blamed for the rupture in this case.

Case 5. Protocol No. 7513 is that of a 66 year old male who was admitted to the hospital because of the sudden onset of retrosternal pain with vomiting and perspiration of two days' duration. On examination he exhibited gallop rhythm but no friction rub. The white blood count was 13,500. He died quite suddenly while being examined, 72 hours after the onset of his pain. On postmortem examination the pericardial sac contained 200 c.c. of blood; heart weight 350 grams; two-thirds of the left ventricle showed recent infarction, in the center of which was a laceration about 3.5 cm. in length. The descending branch of the left coronary artery was completely occluded by old and new thrombi.

Comment: Except for whatever exertion was involved in the process of examination, no apparent cause other than the infarct itself was found for this final episode.

Case 6. Protocol No. 7591 is that of a 79 year old male who suffered from

angina pectoris three months before his admission to the hospital. Six days before admission he was seized, after a walk, with severe precordial pain, only slightly relieved by sedatives. The pain persisted for six days with varying severity. When examined at the hospital, his blood pressure was found to be 150 mm. mercury systolic and 100 mm. diastolic, temperature 99.8° F., pulse rate 110, white blood count 24,000. His electrocardiogram showed changes typical of anterior myocardial infarction. On the third day after his admission, while in bed, he suddenly became cyanotic and died within a few seconds. Postmortem examination revealed 500 c.c. of blood in his pericardial sac; the heart weight was 375 grams and there was an area of infarction about 7 cm. in diameter, in the center of which was a small laceration. The descending branch of the left coronary artery showed a blackish red adherent thrombus.

Comment: No evidence could be obtained to show any cause other than the infarct itself or any premonitory symptoms for this final episode of cardiac rupture.

*Case 7.* Protocol No. 7779 is that of a 62 year old male who suffered from mild angina pectoris for one month previous to a sudden seizure of substernal pain coming after lunch. On examination no friction rub was heard. The blood pressure was 130 mm. mercury systolic and 100 mm. diastolic; pulse rate 72, temperature 102° F. Morphine relieved the pain. Two days later while in bed he was awakened by a severe substernal pain. His pulse rate was 120, white blood count 26,800, temperature 100° F. Gallop rhythm was found. The blood pressure fell to 180 mm. Hg systolic and 75 mm. diastolic. A friction rub was heard after the fifth day of his attack. Temperature and pain continued for a total of 10 days and there were no more subjective symptoms. The patient was resting comfortably in bed and apparently doing well when he was found dead on the fourteenth day after the onset of his illness. Postmortem examination revealed 500 c.c. of blood in the pericardial sac; heart weight 400 grams. There was a recent infarct of the left ventricle, in the center of which was a small laceration. The descending branch of the left coronary artery showed a deep-red soft thrombus and the right circumflex showed a reddish-gray thrombus.

Comment: No cause in the way of special strain could be blamed for this final myocardial rupture.

*Case 8.* Protocol No. 8387 is that of a 67 year old male physician who, for two months before admission, suffered from angina pectoris which had increased in frequency and severity. Two days before admission he suffered severe, continuous substernal pain of two and a half hours' duration. His white blood count was 11,500, pulse rate 84. An electrocardiogram showed signs suspicious of myocardial infarction. He was given fairly heavy sedation for 48 hours, then suddenly became cyanotic and died. Postmortem examination revealed 500 c.c. of blood in the pericardial sac. There was a 1.5 cm. laceration of the left ventricle. The circumflex branch of the left coronary artery was occluded by a grayish-pink granular friable clot.

Comment: Despite heavy sedation in this case cardiac rupture took place.

*Case 9.* Protocol No. 9393 is that of a 51 year old male who was admitted to the hospital with severe crushing substernal pain of two hours' duration. There was no past history of angina pectoris or hypertension. Temperature was 99.6° F., pulse rate 90, blood pressure 130 mm. mercury systolic and 80 mm. diastolic, white count 13,000. No friction rub was heard. An electrocardiogram showed a typical anterior infarction. The pain persisted and twelve hours after admission he suddenly went into collapse and died. Postmortem examination revealed 500 c.c. of blood in the pericardial sac; heart weight 375 grams. There was a 5 cm. area of recent infarction of the left ventricle in the center of which was a 3 cm. laceration. The descending branch of the left coronary artery showed a fresh red-brown thrombus.

Comment: Death from cardiac rupture came quickly and unexpectedly in this patient.

*Case 10.* Protocol No. 9779 is that of a 55 year old male who was seized with attacks of substernal pain radiating down both arms and into the wrists, lasting about one minute, not definitely related to effort, and not affected by nitroglycerine. There were five to 10 attacks each day. An electrocardiogram taken six days after onset was negative. Two and a half weeks after the onset of these seizures he was awakened from sleep with an agonizing substernal pain which lasted five hours. He was given  $\frac{1}{2}$  grain of morphine with relief. Three hours later he developed cyanosis and congestion and 12 hours after the onset of this attack he died. Postmortem examination revealed 1,200 c.c. of blood in the pericardial sac. There was a jagged laceration 3 cm. in length in the left ventricle. There was a soft, thin, flabby area of recent myocardial infarction about 7 cm. in diameter. The descending branch of the left coronary artery showed a gray-red, firmly adherent thrombus 1.3 cm. in length.

Comment: In spite of the negative electrocardiogram this process had probably been going on for a period of two weeks and the terminal episode indicated an extension of the process with myocardial rupture. He had not been confined to bed until the last 12 hours of his life.

### SUMMARY AND CONCLUSIONS

Cardiac rupture occurred in 10 cases, or 3.7 per cent, of a series of 270 instances of myocardial infarction found among nearly 3,000 autopsies at the Massachusetts General Hospital from 1933 through 1940. All 10 cases of cardiac rupture were found among the 105 patients with acute myocardial infarction (9.5 per cent) and none among the 165 cases of old infarction.

The average age of our 10 cases was 65.7 years and the sex incidence was seven males and three females.

Death always ensued quite rapidly after the occurrence of the rupture, as evidenced by the state of the blood in the pericardial sac and the condition of the lacerated tissue.

All 10 deaths occurred in less than two weeks after the clinical onset of acute myocardial infarction, most of them within a period of two to 10 days after the illness began.

In eight of the 10 cases the descending branch of the left coronary artery and the anterior wall of the left ventricle were involved. In one case the circumflex branch of the left coronary was thrombosed and in the remaining case the circumflex branch of the right coronary.

### BIBLIOGRAPHY

1. JETTER, W. W., and WHITE, P. D.: Rupture of the heart in patients in mental institutions, *Ann. Int. Med.*, 1944, xxi, 783-802.
2. MARTLAND, H. S.: Sudden deaths with reference to their prevention, *Proc. New England Heart Assoc.*, 1939-1940, p. 42.
3. EDMONDSON, H. A., and HOXIE, H. J.: Hypertension and cardiac rupture. A clinical and pathologic study of seventy-two cases in thirteen of which rupture of the inter-ventricular septum occurred, *Am. Heart Jr.*, 1942, xxiv, 719.

# RUPTURE OF THE HEART IN PATIENTS IN MENTAL INSTITUTIONS\*

By WALTER W. JETTER, M.D., and PAUL D. WHITE, M.D., F.A.C.P.,  
*Boston, Massachusetts*

THE desirability of recognizing the presence of a myocardial infarct in its earliest stage and of instituting promptly a régime of sedation and bed rest has long been one of the cardinal precepts of clinical practice. It is generally believed that by reducing the physiological demands upon the damaged myocardium to a minimum the danger of rupture is decreased and the likelihood of repair is enhanced.

The postmortem findings in a series of ambulant mentally ill persons in whom sudden collapse and death were unexpected because of absence or perversion of subjective reaction to visceral disease have provided striking confirmation of the importance of early diagnosis and bed rest in the treatment of myocardial infarction. In the series of cases to be reported here-with it was found that 16, or 73 per cent, of a total of 22 patients with acute myocardial infarction died of cardiac tamponade due to rupture at the site of a recent infarct.

*Selection of Material.* Attached to the central administrative organization of the Massachusetts Department of Mental Health is a pathological service for investigating sudden, obscure, and traumatic deaths occurring in mental hospitals. A recent series of 115 consecutive autopsies conducted under the jurisdiction of that service included 69 deaths due to heart disease. Of these obliterative coronary arteriosclerosis was the etiological factor in 61 instances. No visible infarction was evident in 14, whereas in the remaining 47 the following incidence of myocardial infarction was observed: old infarcts only, 25 cases; recent infarcts only, 12 cases; old and recent infarcts combined, 10 cases. Of the 22 hearts containing recent infarcts 16 had ruptured.

*Summary of Cases.* Table 1 summarizes the clinical findings in the 16 cases of cardiac rupture. Ten were male and six were female. The mean age was 66.5 years and in only one instance was the decedent younger than 50.

Routine physical examinations made at periodic intervals in the 16 patients, most of whom had been institutionalized for years, showed a moderate to severe chronic hypertension in 14 instances. In only one case was there a history of previous angina pectoris and in this instance autopsy revealed a healed myocardial infarct (case 2). In 10 instances patients were

\* Received for publication December 23, 1943.

From the Department of Legal Medicine, Harvard Medical School, and Massachusetts Department of Mental Health, and the Cardiac Laboratories of the Massachusetts General Hospital, Boston, Massachusetts.

ambulatory and in apparent good health until they suddenly collapsed and died. In four cases there were vague complaints two to 72 hours prior to death, for which bed rest had been ordered in two instances. These two

TABLE I  
Summary of Clinical Data of 16 Cases of Cardiac Rupture

Case	Sex	Age	Mental Diag.	Length Hosp. Stay (yrs.)	History of Angina Pectoris	Duration of Symptoms before Acute Collapse and Death	History of Hyper-tension	Bed Rest
1	M	72	Imbecile	20	No	3 days (vague)	Yes	Partial
2	M	62	Dem. precox paranoid	21	Yes	None	Yes	None
3	M	77	Alc. psych. Chronic hallucinosis	22	No	11 hrs.	Yes	Complete*
4	F	62	Paranoid condition	12	No	13 hrs.	Yes	Complete*
5	F	67	Dem. precox heb. type	35	No	None	Yes	None
6	M	64	Org. dis. CNS	12	No	2½ hrs.	Yes	None
7	M	64	Dem. precox paranoid	18	No	None	Yes	None
8	F	61	Manic depressive—depressed	16	No	None	Yes	None
9	M	83	Dem. precox paranoid	38	No	None	No	None
10	F	68	Dem. precox paranoid	22	No	None	Yes	None
11	F	63	Dem. precox catatonic	13	No	None	Yes	None
12	F	72	Undiagnosed	0.08	No	None	Yes	None
13	M	67	Epilepsy	40	No	None	Yes	None
14	M	48	Manic depressive—manic	4	No	28 hrs.	No	Partial
15	M	75	Senile psych.	4.5	No	72 hrs.	Yes	Partial
16	M	66	Paranoia	0.5	No	None	Yes	None

\* Bed rest incident to subepicardial hematoma.

individuals died when they got out of bed to go to the bathroom. In the other two cases (cases 3 and 4) there was serious collapse 11 and 13 hours prior to death. This collapse was apparently incident to the development

of a subepicardial hematoma which became progressively larger until its final rupture into the pericardial cavity.

Table 2 summarizes the pathological findings in the 16 cases. Arbitrarily considering a heart to be enlarged if its weight exceeded 400 grams in the male and 350 grams in the female, seven of the 10 male and four of the six female hearts were hypertrophied. The site of the acute infarct involved the left ventricle alone in eight instances, the left ventricle and interventricular septum in seven instances, and both the left and right ventricles and the interventricular septum in the sixteenth case. The infarcts were characteristically large and averaged 4 to 5 centimeters in diameter. In appearance they were soft, friable, and usually a mottled yellow-red, with hemorrhagic foci close to the site of perforation. An early fibrinous pericarditis was present in 10 instances, and endocardial thrombi were present in nine.

The ruptures were usually in the centers of the most recent infarcts and were situated in the left ventricle in 15 instances and in the right in one. The margins of the defects were ragged, hemorrhagic, and friable. Occasionally there were multiple defects in close relation to each other. Although there was always some subepicardial hemorrhage, hematomas of significant size were observed in only three instances (cases 3, 4, and 5).

Multiple blocks of myocardium were taken for histological examination in 15 of the 16 cases. They were stained routinely with hematoxylin and eosin, and occasionally with phosphotungstic acid and Van Gieson's connective tissue and Sudan III stains. An estimation of the approximate age of the infarcts was based on an adaptation of the criteria of Mallory, White, and Salcedo-Salgar.<sup>1</sup> Stage 1 included lesions characterized by early coagulation necrosis of the myocardium with little or no exudation. These were regarded as being less than 24 hours old. Stage 2 comprised lesions in which the necrotic muscle was infiltrated by polymorphonuclear leukocytes. These infarcts were considered to be between one and six days old. Infarcts showing active fibroblastic repair were placed in Stage 3 and were considered to be between one and three weeks in age. In Stage 4 were assigned infarcts cicatricial in character.

In judging the age of an infarct it is essential that the proper sites for histological examination be selected. Healing begins on the periphery of the lesion, proceeding from contiguous living tissue, and then gradually extends inward. During the early weeks as the healing reparative process continues, it is usually the case that different phases are present in different parts of the infarct, that of greatest age occurring at the periphery. Significant sections, therefore, should be taken from the margin of the infarct, and for the purpose of orientation it is preferable that adjacent uninvolved myocardium be included.

Not only do different regions of the same infarct show differences in completeness of destruction and extent of repair but there is always a pos-



TABLE II  
Summary of Autopsy Data of 16 Cases of Cardiac Rupture

Case	Age	Sex	Ht. Wt. (gms.)	Site Recent Infarction	Size Infarct. Dia. Cms.	Site of Defect	Epica-dial Fibrin	Endocardial Thrombi	Old Infarction	State of Coronary Arteries				Microscopic Examination		Complicating Cardiac Lesions	Significant Subepicardial Hemorrhagic Extravasation	Acute Cardiac Aneurysmal Dilatation
										Fresh Thrombus	Organized Thrombus	Hemorrhagic Into Atherosclerotic Plaque	Obstructing Sclerosis without Occlusion	Number of Recent Infarcts Contiguous with Site of Rupture	Estimated Age of Most Recent Infarct			
1	72	M	540	LV IVS	7	LV	+	+	0	—	DRLC	DRLC	DRLC CRLC	Single	1-2 wks.	Aortic insuf- ficiency	0	0
2	62	M	570	LV	3.5	LV	+	+	+	CRLC CRRC	DRLC	—	All	Multiple	2-6 days	None	0	0
3	77	M	460	LV IVS	4-5	LV IVS	0	+	+	DRLC	DRLC RC	—	DRLC CRLC	Single	2-6 days	Aortic stenosis	+	0
4	62	F	420	LV	2	LV	0	+	0	—	RC CRLC	—	RC LCA DRLC	Single	1-2 wks.	None	+	0
5	67	F	550	IVS LV	8	LV	0	0	0	CRLC	CRLC DRLC	—	All	Single	2-4 days	Mitral stenosis. Extensive peri- cardial syne- chia	+	0
6	64	M	520	IVS LV	9	LV	+	+	0	DRLC	DRLC CRLC	—	DRLC CRLC	Multiple	2-4 days	Aortic and mi- tral insuffi- ciency	0	+
7	64	M	440	IVS LV	8	LV	+	+	+	DRLC	DRLC RC	—	RC DRLC DRRC	Single	1-2 wks.	None	0	+
8	61	F	300	LV	5	LV	0	+	0	—	—	—	RC DRLC	Single	2-6 days	None	0	0

LV—left ventricle.  
RV—right ventricle.  
IVS—interventricular septum.  
LCA—left coronary artery.

DRLC—descending ramus left coronary artery.  
CRLC—circumflex ramus left coronary artery.  
CRRC—circumflex ramus right coronary artery.  
DRRC—descending ramus right coronary artery.

TABLE II—Continued

Case	Age	Sex	Ht. Wt. (gms.)	Site Recent Infarction	Size Infarct. Dia. Cms.	Site of Defect	Epicardial Fibrin	Endocardial Thrombi	Old Infarction	State of Coronary Arteries				Microscopic Examination		Complicating Cardiac Lesions	Significant Hemorrhagic Subepicardial Extravasation	Acute Cardiac Aneurysmal Dilatation
										Fresh Thrombus	Organized Thrombus	Hemorrhage into Atherosclerotic Plaque	Obstructing Sclerosis without Occlusion	Number of Recent Infarcts Contiguous with Site of Rupture	Estimated Age of Most Recent Infarct			
9	83	M	350	RV IVS LV	4	RV	0	0	0	DRLC	—	—	RC DRLC	Single	2-4 days	Mitral stenosis	0	0
10	68	F	340	IVS LV	3	LV	+	0	+	—	—	—	DRLC RC	Single	2-4 days	None	0	0
11	63	F	475	LV	4	LV	+	+	0	—	DRLC CRLC	—	RC DRLC CRLC	Multiple	2-4 days	None	0	0
12	72	F	475	LV	4	LV	+	+	+	RC DRLC CRLC	DRLC	—	All	Single	2-3 wks.	None	0	+
13	67	M	300	LV	5	LV	+	0	0	—	DRLC	—	RC DRLC	—	—	None	0	0
14	48	M	360	LV	5	LV	+	0	0	—	—	—	DRLC CRLC	Single	1-2 wks.	None	0	0
15	75	M	500	LV	6	LV	0	0	0	CRLC	—	CRLC	CRLC DRLC CR	Single	2-4 days	None	0	0
16	66	M	510	LV IVS	5	LV	+	0	0	—	—	—	CRLC DRLC	Single	2-3 wks.	None	0	0

sibility that additional infarction has occurred in a region of previous infarction. Such areas may be detected in the type of reparative process.

Assuming the presence of a single large infarct it should be appreciated that it is not always possible to secure sections which include normal muscle, periphery of infarct, and enough of the more centrally located regions to observe the gradual transition in the age of the reparative process. Particularly is this made difficult by the fact that the periphery of an infarct is usually composed of a number of finger-like projections which interdigitate with projections of normal myocardium. Hence a cross section through such an area might show alternating ovoid or circular areas of normal and infarcted muscle.

In the 15 cases in which microscopic examinations were made the site of rupture in 12 apparently represented a single episode of infarction, whereas in three the rupture occurred at the site of mixed acute and less recent infarct. Of the 12 hearts in which rupture occurred at the site of a single episode of infarction four were estimated to be between two and four days old, two were between two and six days in age, four between one and two weeks, and the remaining two cases were between two and three weeks old. Of the three cases in which infarcts of different ages were recognized at the site of rupture there were two in which the most recent infarct appeared to be from two to four days old and one from two to six days old.

#### CASE REPORTS

*Case 1. History.* The deceased was an imbecilic white male of 72 years who had resided in state institutions for 20 years. He was known to have had hypertension for years and during the past two years the systolic pressure had been continuously above 200 mm. mercury.

Three days before death he complained of epigastric pain and vomited once. Examination revealed a tender but nonspastic abdomen. He was put to bed but allowed toilet privileges. Forty-eight hours later no improvement was noted and he was transferred to an infirmary ward. On the third day of illness an attendant observed the patient staggering while returning from the toilet. Suddenly he collapsed, fell to the floor, and upon examination was found to be dead.

*Pathological Examination.* The pericardial cavity contained an estimated 500 c.c. of fluid and fresh blood clot. The heart weighed 540 grams and was the site of an extensive mottled yellow-red soft and friable infarct which involved the lower half of the anterior left ventricular wall and a corresponding area of the interventricular septum which extended around on the posterior wall of the left ventricle for 2 to 3 cm. In the lower half of the infarct near the apex there was an irregular ragged longitudinal linear defect which extended downward and outward from ventricular to pericardial cavity. On the epicardial surface was a thin film of fibrin.

The anterior descending branch of the left coronary artery was the seat of severe sclerosis. One centimeter from its origin there was a segment 3 to 4 mm. long in which the lumen was completely compressed by a fresh hemorrhage into an atherosclerotic plaque. Below this was another segment the lumen of which was occupied by an organizing grayish-brown thrombus. The left circumflex branch showed less marked sclerosis, while the right coronary artery was not significantly involved.

Microscopically the acute infarct was found in myocardium which was the site

of focal scarring. There were large areas of coagulative necrosis peripherally infiltrated by polymorphonuclear leukocytes, most of which had sharply outlined nuclei. Other regions of the infarct chiefly near the endocardial surface showed necrotic polymorphonuclears. Peripherally there were small foci of invasion by young fibroblasts and capillaries in which muscle fibers were in a more advanced stage of dissolution. Only a rare pigmented macrophage was encountered.

*Case 2. History.* The deceased was a white male of 62 years who had been a patient for 21 years, the mental diagnosis being dementia praecox of paranoid type. Eight months before death a clinical diagnosis of acute myocardial infarction had been made and his name had been placed upon the danger list. Following a period of bed immobilization there was apparent recovery. The heart was considered enlarged and the blood pressure was 160 mm. Hg systolic and 90 mm. diastolic.

Immediately prior to his death the deceased appeared well physically and carried out his usual activities. Suddenly, while walking about on the hospital grounds, he collapsed and fell to the sidewalk, sustaining lacerations of the head. When he was examined by a physician he was found to be dead.

*Pathological Examination.* The pericardial cavity was distended with freshly clotted blood. The heart weighed 570 grams. Midway between apex and base the lateral wall of the left ventricle was the site of a mottled yellow-red soft and friable infarct 3.5 cm. in diameter. On the underlying endocardium were small recent thrombi, while on the epicardium was a thin layer of fibrin. There was a diagonal linear ventricular defect in the approximate center of the infarct. The defect began posteriorly from the endocardial surface and by thin linear slices was traced anteriorly and upward to its point of exit on the lateral surface of the left ventricle.

The myocardium of the interventricular septum and left ventricular wall near the apex was replaced in large foci by dense cicatrization.

The coronary arteries were the seat of severe arteriosclerosis. The left anterior descending artery showed obliterating disease by continuous hyaline and calcific subintimal plaques. At a point approximately 2 centimeters from its origin the vessel was obliterated by a gray-brown mass. One and one-half centimeters from its origin the lumen of the left circumflex artery appeared completely obliterated by a soft red mass. The right coronary artery showed moderately severe arteriosclerosis and its descending ramus likewise revealed a lumen occupied by a fresh thrombus.

Noncardiac significant abnormalities outside the heart included severe atherosclerosis of the aorta and moderate cerebral arteriosclerosis and arteriolar nephrosclerosis.

Microscopically at the site of rupture there appeared to have been two distinct recent infarcts which occurred in atrophic muscle fibers separated by loose collagen deposit. The first infarct was in a state of recent necrosis and showed minimal infiltration by polymorphonuclear leukocytes. In direct relation there was an abrupt transition to a lesion in which almost all of the myocardium had been removed, its site being occupied by organizing connective tissue containing a few macrophages (figure 1).

*Case 3. History.* The deceased was a white male of 77 years who had been a patient in a state mental institution for 22 years. The mental diagnosis was alcoholic psychosis with chronic hallucinosis. Eighteen months before death a diagnosis of aortic stenosis had been made by the medical service of the hospital. Somewhat later attacks of syncope associated with a slow pulse occurred and a diagnosis of Adams-Stokes syndrome was made. Fourteen months before death the blood pressure was 200 mm. Hg systolic and 120 mm. diastolic; succeeding readings were similarly elevated.

On the day of death at 5:15 a.m. the deceased fainted while walking to the toilet

and fell to the floor, sustaining a contusion of the left forehead. He was put to bed. In the afternoon there was a slight fever. He died unexpectedly in bed at 4:45 p.m.

*Pathological Examination.* The pericardial cavity was distended with blood. The heart weighed 460 grams. On the anterior surface over the interventricular septum and about 2 centimeters from the apex there was a slightly curved vertical linear defect with ragged edges 1.5 centimeters in length (figure 2). The anterior wall of the left ventricle and the interventricular septum over an area of 4.5 centimeters in diameter near the apex was thinned, mottled yellow-red, and soft. On the endocardial surface were recent thrombi. Examination by linear slicing showed two irregular ragged tears running through the myocardium in close approximation to each other; they converged outward. The more medial of the two proceeded through



FIG. 1. Photomicrograph taken from region of rupture in case 2. There appear to be infarcts of two distinct ages. In the lower half of the photomicrograph, the heart muscle is the seat of acute necrosis and is invaded by but few polymorphonuclear leukocytes. From this approximately 2 day old infarct there is an abrupt transition to the lesion occupying the upper half of the photograph in which the myocardium has been replaced by organizing and richly vascularized connective tissue. A few macrophages remain. This infarct was judged to be at least 3 weeks old. H & E  $\times 150$ .

the left lateral margin of the interventricular septum. The subepicardium in relation to the defect was the seat of significant hemorrhage.

Beginning at the apex on the posterior wall of the left ventricle were large foci of dense cicatrization over an area 3.0 centimeters in diameter.

The aortic valve was a rigid non-elastic structure and the thickened, rigid and retracted cusps formed a slit-like orifice 1.2 centimeters long and 2 millimeters wide. There was also a chronic valvulitis of the mitral valve which had not apparently impaired its functional efficiency.

The coronary arteries were the seat of severe arteriosclerosis. The anterior descending branch of the left coronary artery showed severe segmental obstructing sclerosis by hyaline and calcific subintimal plaques. There were two areas in the

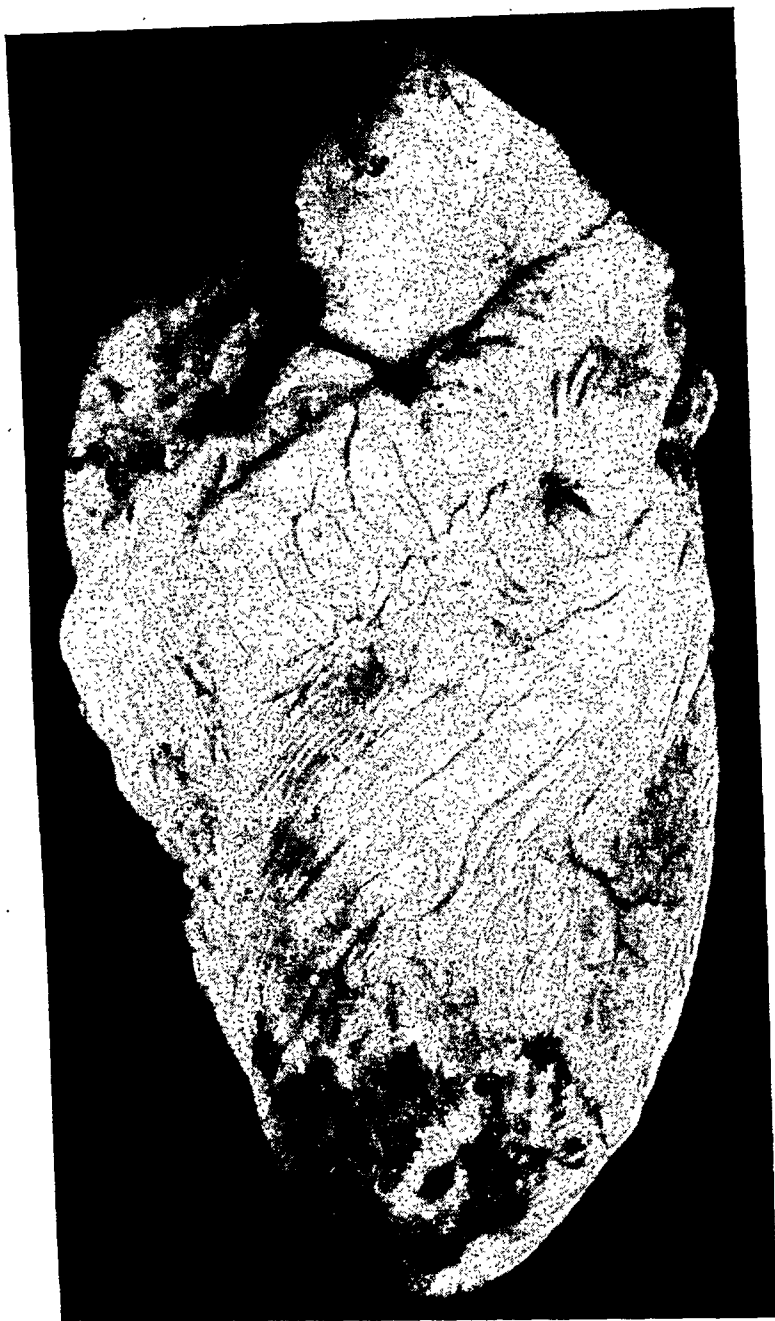


FIG. 2. Anterior aspect of the heart in case 3. The site of the rupture on the epicardial surface is located close to the apex on the anterior surface of the heart over the interventricular septum. Note the subepicardial hematoma in relation to the defect.

vessel—in which the lumen was obstructed, one by an organizing grayish-brown thrombus and the other by a jelly-like red mass. The right coronary artery was the site of severe arteriosclerosis; its lumen was obstructed by an old thrombus about 4 centimeters from the orifice.

In addition to the findings in the heart there were moderate arteriolar nephrosclerosis and severe atherosclerosis of the aorta.

Microscopically a single recent infarct was observed, in relation to the rupture,

in myocardium which was the site of small focal scars. The infarct showed extensive necrosis and its outer portions were infiltrated with numerous polymorphonuclear leukocytes, most of which were degenerating. Penetrating the infarct at its periphery were occasional blood capillaries and a few fibroblasts.

*Case 4. History.* The deceased was a white female of 62 years with a mental diagnosis of paranoia. She had been a patient in a mental institution for 12 years. She was moderately obese and showed severe hypertension (250 mm. Hg systolic and 120 mm. diastolic) and moderate cardiac hypertrophy.

The night before death at 7:00 p.m. the patient complained of being abused and persecuted but did not mention physical complaints. Shortly thereafter she was found unconscious. She regained consciousness after the administration of stimulants, then again became unconscious, and died about 13 hours after her original complaint.

*Pathological Examination.* The heart weighed 420 grams. There was extensive subepicardial hemorrhage over the lower anterior aspect of the left ventricle extending medially to include the anterior surface of the interventricular septum. Slightly to the right of the apex of the left ventricle there was a small irregular defect in the epicardium from which blood could be expressed. Thin linear sections showed the myocardium of the anterior and lateral wall of the apex of the left ventricle to be a mottled gray and yellow, in places hemorrhagic, and extremely friable. Through this infarct there extended a small irregular laceration partially obscured on the endocardial surface by a small friable gray mural thrombus.

The coronary arteries were the seat of severe sclerosis and in the midportion of the circumflex ramus of the right coronary artery there was complete occlusion by a grayish-yellow firm mass. Proximal to this occlusive mass there were two small patent branches. For a short distance distal to the occlusion the artery was represented by a slender fibrous cord. There was severe intimal sclerosis of the left coronary artery between the ostium and its bifurcation. Near the origin of the left descending ramus there was a segment of almost complete occlusion in which the lumen was reduced to less than 1 millimeter in diameter. A segment occluded by grayish-yellow non-calcified material was found in the major oblique branch of the left circumflex artery.

There was moderate arteriolar nephrosclerosis.

Microscopically the margins of the acute myocardial infarct were infiltrated by young granulation tissue, numerous pigment-containing macrophages, some plasma cells, and a few eosinophiles. The central mass of the infarct showed necrosis of the muscle and infiltration with varying numbers of polymorphonuclear leukocytes.

*Case 5. History.* The deceased, a white female of 67 years, whose mental diagnosis was dementia praecox, hebephrenic type, had been a patient in a mental institution for 35 years. She had been paroled into a family-care home for several years, returning to the hospital at stated intervals for examination. The last routine physical examination revealed an enlarged heart and a blood pressure of 180 mm. Hg systolic and 110 mm. diastolic but no other noteworthy findings.

While in her room at the private home early in the morning she is said to have collapsed and fallen to the floor. She was pronounced dead when a physician arrived.

*Pathological Examination.* The posterior portion of the pericardial cavity was distended by between 150 and 200 c.c. of dark purple clotted blood and here the subepicardium was the site of a fresh hematoma up to 1 centimeter thick. Thin fibrous adhesions between pericardium and epicardium completely obliterated the pericardial cavity anteriorly. The subepicardial fat was uncommonly thick throughout, measuring 2.5 centimeters thick at the base and 1.5 centimeters at the apex. There was an eccentric hypertrophy of the left auricle and of the right ventricle and auricle. The mitral valve was the seat of an important stenosis. Superimposed upon the auricular

surface of the thickened mitral valve leaflets close to the free edge there was a row of small fresh granular vegetations.

The posterior wall of the left ventricle from apex to base and the posterior part of the interventricular septum were soft, friable, and a mottled yellow-red. On the epicardial surface midway between apex and base were a series of small defects covering an area 2 centimeters in diameter. With appropriate sections multiple ragged and irregular defects were found traversing infarcted myocardium from endocardial to pericardial cavity (figure 3).



FIG. 3. Longitudinal sections through the posterior wall of the left ventricle (case 5). The upper two-thirds of the ventricular wall is the seat of an acute infarct. Note the large subepicardial hematoma, also the fresh thrombus occupying the lumen of the concentrically narrowed circumflex ramus of the left coronary artery in the photograph to the right.

The coronary arteries were the seat of severe arteriosclerosis and there were continuous hyaline and calcific subintimal patches along their course. The lumen of the anterior descending branch of the left coronary artery showed in its first 3 centimeter segment a lumen completely closed by firm grayish-yellow material. There was similar segmental occlusion in the circumflex ramus which was distal to an occlusion by a gelatinous red mass close to the origin of the vessel. The right coronary artery showed segmental obstructing sclerosis but no occlusion.

Other pathological abnormalities included severe arteriolar nephrosclerosis and ovarian adenofibromata.



The coronary arteries were the seat of severe sclerosis. The left coronary artery showed severe concentric calcification. The anterior descending ramus showed 3 centimeters from its origin a lumen completely occluded by fairly firm yellow-gray material in a 1 centimeter segment and beyond this the lumen was completely closed by a dark purple-red mass. Two rather large branches arising from the anterior descending artery showed similar recent thrombosis. The right coronary artery at the lateral margin of the heart showed occlusion by a grayish-brown somewhat friable mass. The left circumflex artery was patent but also showed moderately severe disease.

There were also an inconsequential healed mitral and aortic valvulitis and moderate arteriolar nephrosclerosis.

Microscopically the acute infarct occurred in an area in which the muscle fibers were atrophic and separated by thin strains of collagen. There was a large central mass of necrotic muscle and its outer portion was infiltrated by large numbers of necrotic polymorphonuclear leukocytes. At the periphery was minimal invasion by fibroblasts and capillaries. A moderate number of microphages was present.

*Case 8. History.* The deceased, a white female of 61 years with a mental diagnosis of manic depressive psychosis, depressed type, had been institutionalized for 16 years. During this time routine physical examinations had been essentially negative except for mild chronic hypertension.

Three days before death she stated to her doctor that she had what she thought was indigestion with epigastric pain and distress in her back. She further stated that she frequently had these attacks and would soon be better. No abnormalities being found, she was given phenobarbital for sedation and slept. She continued to be ambulatory and there were no further complaints until three days later when she went to the bathroom and while washing her face suddenly slumped to the floor and died.

*Pathological Examination.* The pericardial cavity was distended with fresh blood clot. The heart weighed 300 grams. On the anterior wall of the left ventricle two-thirds of the distance from apex to base there was a stellate defect 1.8 centimeters in diameter which communicated with the ventricular cavity by an irregular channel having blood stained and friable walls. The defect was in the approximate center of an acute infarct 5 centimeters in diameter having a mottled yellow-red color. The overlying epicardium had a thin film of fibrin on its surface. There were no other significant abnormalities.

The coronary arteries showed severe obliterating sclerosis but no complete occlusions. The points of extreme narrowing were in the right coronary artery close to its orifice and in the descending ramus of the left coronary also close to its origin. The vessels throughout showed both eccentric and concentric disease with hyaline and calcific plaques predominating.

The kidneys showed moderately severe arteriolar sclerosis.

Microscopically at the site of the rupture the infarcted myocardium was necrotic and infiltrated with many polymorphonuclear leukocytes. Its periphery was invaded by a few capillaries and deeply-basophilic fibroblasts. An occasional fiber had undergone phagocytosis.

*Case 9. History.* The deceased was a white female of 83 years. Her mental diagnosis was dementia praecox, paranoid type, and she had resided in the hospital for 38 years. Routine physical examination had shown the presence of a loud blowing systolic heart murmur for many years, but there were no other noteworthy physical findings.

The patient resided on a ward for chronic ambulatory patients and on the day of death arose as usual and ate breakfast. After leaving the dining room she sat

on a chair in the day hall and suddenly was observed to slip to the floor. She was dead when a supervisor arrived.

*Pathological Examination.* The pericardial cavity was occupied by a fresh blood clot. The heart weighed 350 grams. On the anterior surface of the right ventricle close to the interventricular septum and about 2 centimeters from the apex was a linear defect less than 1 centimeter long which communicated with the right ventricular cavity. In relation to this defect was a soft, friable, and mottled yellow-red acute infarct 4 to 5 centimeters in diameter involving both right and left ventricles and intervening septum.

The mitral valve was the site of a severe stenosis.

The coronary arteries showed occluding hyaline and calcific arteriosclerosis with occluding disease in both right and left anterior descending coronary arteries. The latter vessel about 2 centimeters from its origin was obstructed by a recent brownish-red thrombus.

Microscopically sections of the infarcted myocardium showed large areas of necrosis with little or no exudation. In other areas there was infiltration by large numbers of polymorphonuclear leukocytes, most of which were necrotic.

*Case 10. History.* The deceased was a white female of 68 years who had been a patient in a state hospital for 22 years. Her mental diagnosis was dementia praecox, paranoid type. Five years before death she developed a left hemiplegia from which she made a partial recovery and subsequently became partially ambulatory.

On the day of death, while eating her luncheon, she suddenly became cyanotic, collapsed, and was dead upon examination.

*Pathological Examination.* The pericardial cavity contained fluid and clotted blood. The heart weighed 340 grams. Immediately adjacent to the interventricular septum close to the apex there was a small vertical linear defect less than 1 centimeter long in the left ventricle which communicated with the ventricular cavity. On the epicardial surface there was a thin soft film of fibrin. In relation to the defect the myocardium over an area roughly 3 centimeters in diameter was soft, friable, and a mottled yellow-red. There were numerous scattered foci of myocardial scarring in the left ventricle and interventricular septum posteriorly near the apex.

The coronary arteries showed severe obstructing arteriosclerosis. At a point 1 centimeter from its origin the lumen of the descending ramus of the left coronary artery was completely closed by a red mass. There was also severe occluding sclerosis in the same vessel and in the right coronary artery with eccentric hyaline and calcified subintimal plaques.

There were moderate arteriolar nephrosclerosis and cerebral arteriosclerosis and an old infarct involving the right internal capsule.

Microscopically the acute myocardial infarct showed simple necrosis of the myocardium and an early reactive phase consisting chiefly of infiltration by polymorphonuclear leukocytes.

*Case 11. History.* The deceased, a white female of 63 years with a mental diagnosis of dementia praecox, catatonic type, had been a patient in the institution for 13 years. Throughout her hospital stay she had shown severe hypertension and was always obese. There was no history of cardiac failure.

In the afternoon of the day of death she was sitting on a sun-porch together with other patients. It was observed by an attendant that the patient had slumped forward in her chair and when she was placed back in a sitting position it was obvious that she was dead.

*Pathological Examination.* The pericardial cavity contained from 500 to 700 c.c. of blood clot, mostly fresh. The heart weighed 475 grams. There was an epicardial defect posteriorly on the left ventricle 1.0 centimeter from the apex. The surrounding epicardium was dulled by fibrin. Communication with the ventricular

cavity could be easily demonstrated and the walls of the laceration were friable and blood stained. In relation to the defect there was an acute infarct 4 centimeters in diameter, which was mottled yellowish-red and somewhat thinned. Adherent to the endocardium and partially obscuring the defect were recent thrombi.

The coronary arteries were injected according to the method of Schlesinger and showed extensive obliterating arteriosclerosis with numerous old occlusions chiefly in the anterior descending and left circumflex artery.

The kidneys showed moderate arteriolar sclerosis, and the Circle of Willis was the site of small miliary aneurysms up to 1 millimeter in diameter, none of which showed evidence of rupture.

Microscopically at the site of rupture there appeared to be two distinct infarcts, both of recent origin. The most recent of the two showed simple necrosis and moderate infiltration of its outer part by degenerating polymorphonuclear leukocytes. The second infarct was in immediate relationship to the first and was characterized by an abrupt transition in the type of reaction to one of moderately well advanced organization in which thin strands of collagen were present.

*Case 12. History.* The deceased was a white female of 72 years who died 23 days after admission to the hospital. Her routine physical examination on admission showed no significant physical abnormalities except for a blood pressure of 175 mm. Hg systolic and 100 mm. diastolic.

On the day of death the deceased was brought to an examining room for a routine pelvic examination. At that time it was noted by a physician that she exhibited some dyspnea. An examination of the heart was made and showed no abnormalities. The pulse was normal. However, the pelvic examination was not performed and the patient was allowed to sit in a chair while the physician examined another patient. Suddenly it was observed that the deceased collapsed; upon examination she was found to be dead.

*Pathological Examination.* The pericardial cavity was occupied by approximately 500 c.c. of fluid and freshly-clotted blood. There was an area of apical bulging 4.0 centimeters in diameter with thin subepicardial hemorrhagic infiltration. Just above the apex anteriorly there was a ragged stellate defect at the lower margin of which the pericardium was loosely adherent. When thin linear slices were made through the heart it was found that the apical bulging had resulted from aneurysmal dilatation at the seat of an acute myocardial infarct. The ventricular wall varied from 3 to 4 millimeters thick, was soft and friable, mottled yellowish-red, and showed numerous small hemorrhagic foci. The aneurysmal space itself was occupied by endocardial thrombi on the surface of which was fresh blood clot. Continuous with the acute infarct on the anterior left ventricle the myocardium had in great part been replaced by scar tissue.

The coronary arteries were the site of severe arteriosclerosis. The left had a lumen moderately narrowed by atheromatous deposit. The anterior descending artery was completely occluded by an organizing yellowish-gray thrombus over a segment 1.0 centimeter in length beginning at a point 1.5 centimeters from the origin of the vessel. Below the organizing thrombus the artery was completely closed by a firm dark red mass. Two branches of the anterior descending artery were similarly occluded. At a point 1.5 centimeters from its origin the circumflex ramus of the left coronary artery was completely occluded by a firm dark red mass. The right coronary artery was patent for the first 3.0 centimeters although the site of severe sclerosis. Beyond this the vessel was completely occluded by a dark red firm mass.

There was moderate arteriolar nephrosclerosis.

There was a perforated mucocoele of the appendix with an extensive pseudomyxomatous peritonitis.

Microscopically the myocardium in the acute infarct was replaced by young

granulation tissue which in some areas showed thin strands of collagen. There were scattered foci of endothelial leukocytes containing brown pigment and moderate infiltration of polymorphonuclears in relation to a central mass of necrotic myocardium.

*Case 13. History.* The deceased was an epileptic white male of 67 years who had been a patient in state institutions for 40 years. During the last 15 years of life he had shown a hypertension varying from 180 mm. Hg systolic and 100 mm. diastolic to 220 mm. systolic and 120 mm. diastolic.

During the night, 12 hours before death, he had a mild epileptic seizure but was apparently normal thereafter. At noon the following day he suddenly collapsed while in the dining room and was dead upon examination.

*Pathological Examination.* The pericardial cavity was distended by fresh blood clot. The heart weighed 300 grams. Over the anterior left ventricle midway between apex and base there was a small area of recent pericardial adhesions which partially sealed an epicardial defect. In relation to this fibrinous pericarditis the myocardium was the site of an acute soft and friable infarct which was a mottled yellow-red in color. Through the approximate center of the infarct passed an irregular perforating channel having ragged and blood stained walls.

The coronary arteries showed severe arteriosclerosis with occluding disease in the right and left anterior descending vessels. The latter was also completely occluded by an organizing thrombus close to its origin.

This heart was not studied microscopically.

*Case 14. History.* The deceased was a white male of 48 years, whose mental diagnosis was manic depressive psychosis, manic type. He had resided in a state hospital for the past four years and his routine physical examinations revealed nothing noteworthy.

The day before death at 6:30 a.m. he complained of a sharp pain in his chest. He was given gr.  $\frac{1}{4}$  of morphine and removed to a medical ward. On examination the temperature was found to be 99.6° F., and the patient was irritable in manner, gagging but not vomiting. The pulse was 64 per minute. He slept in naps during the afternoon and night and the following morning felt better. At 7:00 a.m. he had taken fluids. He was seen by a physician at 9:00 a.m. and looked better. At 10:30 a.m. he got out of bed and walked to the bathroom. Two other patients stated that he slumped to the floor and collapsed after walking two steps. A physician pronounced death at 10:40 a.m.

*Pathological Examination.* The pericardial cavity was occupied by blood clot. The heart weighed 360 grams. Midway between apex and base over the left ventricle there was a ragged  $0.8 \times 0.3$  centimeter defect which communicated with the left ventricular cavity. Above this perforation there was a slightly smaller defect which was also complete and communicated with the ventricular cavity. The walls of both defects were ragged, friable, and blood stained. The surrounding epicardium was covered with fibrin. Over an area approximately 5.0 centimeters in diameter the myocardium was the site of an acute infarction and was soft, friable, slightly thinned, and a mottled reddish-yellow with numerous hemorrhagic foci.

The coronary arteries showed extensive arteriosclerosis but no complete occlusion. There was severe obliterating disease by eccentric hyaline and calcific plaques in the descending and circumflex rami of the left coronary artery.

Microscopically there was seen extensive infiltration of necrotic myocardium by polymorphonuclear leukocytes, most of which were necrotic. There were occasional pigment-containing phagocytes and a minimal attempt at repair by peripherally invading young granulation tissue.

*Case 15. History.* The deceased was a white male of 75 years who had been a patient at the mental institution for four and a half years. The mental diagnosis was

senile psychosis, paranoid type. Routine physical examinations showed chronic hypertension and cardiac hypertrophy.

Three days before death he suddenly collapsed while at supper. Approximately 10 minutes later he appeared resting comfortably. When questioned by a physician he complained of pain in the umbilical region extending downward into the right lower quadrant. Examination of the abdomen revealed no abnormalities. The pulse was said to have been weak but examination of the heart revealed no abnormalities. Subsequently he appeared in no discomfort and was up and about. On the day of death, three days later, while at the cafeteria, he was observed suddenly to become cyanotic and to fall to the floor. He was dead when examined.

*Pathological Examination.* The pericardial cavity contained an estimated 500 to 700 c.c. of fresh blood clot. The heart weighed 500 grams. On the back of the left ventricle midway between apex and base and about 1.5 centimeters from the interventricular septum there was a slightly diagonal vertical defect 1.5 centimeters long which communicated directly with the left ventricular cavity. The walls of the defect were friable, soft, and blood stained. The perforation was in the approximate center of the large (6.0 centimeters in diameter) infarct showing slightly thinned, soft, and friable muscle discolored a mottled yellow-red. There were small foci of hemorrhage scattered throughout.

The coronary arteries were injected according to the method of Schlesinger and were found to have been the site of severe arteriosclerosis. In the circumflex ramus of the left coronary artery there were recently occluded segments and in one place the lumen was compressed by hemorrhage into an atherosclerotic plaque. The right coronary and the descending ramus of the left showed segments in which the lumina were severely narrowed.

There was severe arteriosclerosis of the aorta and cerebral arteries. The kidneys showed moderate arteriolar nephrosclerosis.

Microscopically there was a large central area of necrotic myocardium with little exudative reaction. The periphery of the lesion was extensively infiltrated by necrotic polymorphonuclear leukocytes. The infarct occurred in muscle the site of small foci of scarring.

*Case 16. History.* The deceased, a white male of 66 years, with a mental diagnosis of paranoia, had been a patient at the mental institution for about six months. Physically he was moderately obese, and the blood pressure was 210 mm. Hg systolic and 120 mm. diastolic. His general health seemed good and he never complained.

While on the hospital grounds walking from one building to another he suddenly collapsed and in 15 minutes was dead.

*Pathological Examination.* The pericardial cavity was occupied by fresh blood clot. The heart weighed 510 grams. On the anterior wall of the heart, slightly to the left of the interventricular septum there was a large linear vertical defect 2.5 centimeters long which gaped at its mouth to 0.5 centimeter. The external defect was found to communicate with the left ventricular cavity by means of a ragged blood stained channel. In relation to the perforation the myocardium was the site of an acute infarct over an area roughly 5.0 centimeters in diameter. The interventricular septum was involved in the process. The infarcted myocardium was soft, friable, slightly thinned, and a mottled yellow-red.

The descending and circumflex rami of the left coronary artery showed occluding arteriosclerosis, most marked in the former branch. The right coronary artery was less severely involved.

Microscopically the infarct in relation to the rupture showed a moderately advanced stage in the removal of muscle fibers and replacement by granulation tissue containing a small amount of collagen. There were considerable numbers of pig-

ment-containing macrophages and varying numbers of polymorphonuclear leukocytes, plasma cells, and eosinophiles. The former were found in a centrally located mass of necrotic muscle.

### DISCUSSION

Although spontaneous rupture of the heart through a fresh myocardial infarct is an occasional finding by the coroner in his postmortem examination of individuals who die unexpectedly, as noted by Martland who found 42 such cases (13.8 per cent) among 304 instances of coronary occlusion in a series of 2,000 autopsies,<sup>2</sup> the percentage of ventricular ruptures in the present series (73 per cent) is by far the highest that we have known about. It is especially interesting and instructive to compare it with the percentages of cardiac ruptures encountered in the wards of general hospitals, for example, 8 per cent (72 cases among 865 of unhealed myocardial infarcts) at the Los Angeles County Hospital<sup>3</sup> and 9.5 per cent (10 cases among 105 of fresh myocardial infarcts) at the Massachusetts General Hospital.<sup>4</sup> As a rule the cases found in the general hospitals entered the wards with the diagnosis already made and so, with their own intelligent and vital cooperation, were treated by complete bed rest and other necessary measures in the most approved manner; despite that fact there were hearts that ruptured, owing in the main to the severity of the disease, perhaps an almost irreducible minimum.

Apropos of the general subject of medical diagnosis and care in the mentally ill, it should be observed that difficulties are encountered not ordinarily present in the general community. Frequently the psychotic individual does not complain even though he is desperately sick. Particularly is this so in the chronic mental patient who has deteriorated intellectually. It will be observed that this was the type of individual which predominated in the present series. It has been our experience that many mentally ill persons do not complain even though they are the victims of severe degenerative or infectious disease. Moreover, even though they do complain, their symptoms are likely to be so bizarre and distorted that their significance is likely to go unrecognized. Although mental institutions are fully aware of these difficulties and train their ward personnel to detect and report seemingly insignificant behavior changes in their charges, it remains a fact, however, that all too frequently the physician is confronted with the task of making a medical diagnosis by objective findings alone.

### SUMMARY AND CONCLUSIONS

1. In a series of 115 consecutive autopsies of patients who died suddenly or unexpectedly in Massachusetts Mental Institutions 16, or 73 per cent, of a total of 22 cases of acute myocardial infarction showed cardiac tamponade due to rupture of the heart wall at the site of the recent infarct.

Cardiac rupture was not found in any of the 25 cases in the same series with healed infarct only.

2. The psychiatric diagnoses were dementia praecox in six cases, manic depressive psychosis in two, paranoia in two, alcoholic psychosis in one, senile psychosis in one, epilepsy in one, imbecility in one, organic disease of the central nervous system in one, and undiagnosed in one.

3. The mean age of the 16 persons whose hearts ruptured was 66.5 years, slightly less than one year older than the average age in Friedman and White's series.<sup>4</sup> Ten were males and six females:

4. Fourteen of the 16 patients had shown a moderate to severe hypertension in past years. In only one case was there a definite history of angina pectoris.

5. Ten of the patients were ambulatory and in apparent good health before their sudden collapse and death. Four patients had complained mildly and two of these received partial-bed rest. The remaining two persons were incapacitated during the approximate last 12 hours of life incident to the development of an extensive subepicardial hematoma. A definite antemortem diagnosis of myocardial infarction or cardiac rupture was not made in any of the cases.

6. The acute myocardial infarct, through which the rupture occurred, was located in the left ventricle in eight instances (anterior wall five, posterior wall two, lateral wall one), both left ventricle and interventricular septum were involved in seven cases, and in the sixteenth case both ventricles and the intervening septum were included. Early fibrinous pericarditis was present in 10 and endocardial thrombosis in nine. The ruptures involved the left ventricular wall in 15 cases and the right in one.

7. The estimated age of the responsible infarct was two to four days in six cases, two to six days in three cases, one to two weeks in four cases, two to three weeks in two cases, and not stated in the remaining case.

8. This experience, in contrast to that in ordinary medical practice where it is possible to make early diagnoses and to institute adequate treatment, strongly supports the present approved therapy of bed rest during the first three weeks after the onset of acute myocardial infarction.

#### BIBLIOGRAPHY

1. MALLORY, G. K., WHITE, P. D., and SALCEDO-SALGAR, J.: The speed of healing of myocardial infarction, *Am. Heart Jr.*, 1939, xviii, 647.
2. MARTLAND, H. S.: Sudden deaths with reference to their prevention, *Proc. New England Heart Assoc.*, 1939-1940, p. 42.
3. EDMONDSON, H. A., and HOXIE, H. J.: Hypertension and cardiac rupture. A clinical and pathologic study of seventy-two cases in thirteen of which rupture of the interventricular septum occurred, *Am. Heart Jr.*, 1942, xxiv, 719.
4. FRIEDMAN, S., and WHITE, P. D.: Rupture of the heart in myocardial infarction. Experience in a large general hospital, *Ann. Int. Med.*, 1944, xxi, 778-782.

# KEROSENE INTOXICATION \*

By W. B. DEICHMANN, PH.D., K. V. KITZMILLER, M.D., F.A.C.P.,  
S. WITHERUP, B.S., and RALPH JOHANSMANN, M.D.,  
*Cincinnati, Ohio*

KEROSENE is a hydrocarbon complex, derived from crude oil or petroleum, used essentially for illuminating and heating purposes. It is composed of fractions of high boiling point (initial 200–350° F., final 500–600° F.) and relatively low volatility, and differs according to the source and consequent composition of the crude oil stocks. These are essentially asphaltic and paraffin-base derivatives, the former containing aromatic and highly unsaturated hydrocarbons. Refining processes usually leave traces of impurities in the finished product. These may be sulfur and nitrogen compounds, caustic alkali, alkaline plumbite solution, organic solvents and adsorbents such as fuller's earth. The kerosenes referred to in the experimental observations reported herein (table 1), were obtained from mid-

TABLE I  
Comparison of the Toxicity of Various Brands of Kerosene  
Administered Orally in One Dose to Rabbits  
The dose in each instance was 28 ml./kg.

Source of Kerosene	Number of Rabbits Used	Per Cent of Deaths
Pure Oil Co.....	20	50
Eureka Oil Co.....	6	66
Tower Oil Co.....	6	0
Re-Go Oil Co.....	6	50
The Texas Co.....	6	66
White Rose.....	6	50
Socony-Vacuum Oil Co.....	6	17
Sinclair Refining Co.....	6	33
Sinclair Refining Co.*.....	6	33
Shell Oil Co.....	6	50
Standard Oil Co.....	6	17
Sun Oil Co.....	6	50
Gulf Oil Corp.....	6	17
Commercial Solvents Corp.*.....	6	0

\* These kerosenes were highly purified for use as bases for insecticide sprays.

continent or Pennsylvania crude oil and were composed primarily of paraffin hydrocarbons and contained only small amounts of naphthenic, aromatic and olefinic compounds.

## ETIOLOGY

In the petroleum industry kerosene intoxication has little importance. Outside the industry it occurs frequently as the result of accidental ingestion usually by infants and children whose ages range from 10 months to three

\* Received for publication April 17, 1944.  
From the Kettering Laboratory of Applied Physiology, and Department of Pathology, Children's Hospital, College of Medicine, University of Cincinnati, Cincinnati, Ohio.



years. These cases of poisoning result from careless household use and storage of the compound and often occur because it is left in glasses, cups and bottles commonly used for milk and other beverages, and placed within the reach of small children. Numerous fatal cases have been recorded among infants and children as the result of swallowing small amounts of kerosene.<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> Among adults, however, susceptibility is apparently much less since no fatal cases are on record despite reports of the ingestion of considerable quantities.<sup>5</sup>

### ACUTE POISONING

*Symptoms and Clinical Findings.* The clinical picture of kerosene intoxication is characterized by both immediate and delayed effects. In the former the irritant action of the liquid is evidenced by burning of the mouth and throat, spasm of the glottis, coughing and choking, substernal and epigastric pain and frequent vomiting. Shortly following absorption, evidence of cerebral depression is manifested by drowsiness, collapse, muscular twitching and coma, usually associated with feeble, rapid pulse, accelerated respiration and moderately elevated temperature. When death is delayed for several days, there is evidence of myocardial insufficiency, hepatic and renal damage, and pneumonia usually terminates the picture. The following case report illustrates the essential points in acute poisoning.

### CASE REPORT

A one-year-old white male child previously in good health and with no history of former illnesses drank a mouthful of kerosene from a bottle found on the floor of his home. Coughing ensued immediately. The mother gave the child soda water by mouth and took him to a physician's office, arriving within 10 minutes. There the stomach was lavaged with two quarts of baking-soda solution. The child was then sent to the Children's Hospital and arrived there in a state of collapse 50 minutes after drinking the fluid.

*Physical Examination.* The child was well developed and well nourished but moribund and cyanotic. The mucous membrane of the nose was congested, the throat intensely reddened, and a distinct odor of kerosene was detected on the breath. The pupils were regular and equal, but reacted sluggishly to light. The heart sounds were weak and rapid. There were no murmurs. Respiration was irregular and gasping. There was impaired resonance over the entire thorax, and many coarse râles and rhonchi were heard throughout all lung fields. The abdomen was distended. The extremities were cold, and the reflexes hypoactive.

*Course in Hospital.* Coramine was administered immediately on admission and within 15 minutes the child was placed in an oxygen tent. Hot water bottles and warm blankets were applied and a continuous infusion of 5 per cent glucose was given intravenously. Suction applied to the throat obtained a moderate amount of mucus. Within two hours after admission the pulse rate was 136, the respiratory rate had risen to 80, and the temperature was 102.2° F. Again suction to the throat recovered a large amount of thick white mucus mixed with bright red blood. Vomiting occurred and the vomitus, which was small in amount, consisted of thick mucus possessing a strong odor of kerosene. The pulse and respiratory rates remained rapid, but for a few hours the cyanosis lessened and almost disappeared, and the child's condition

seemed somewhat improved. The lungs, however, remained full of coarse râles and rhonchi. Sodium luminal was administered to allay restlessness. Six hours after admission the child's condition became worse, cyanosis returned, and throughout the ensuing two hours became progressively more intense. Respirations soon became very shallow and the pulse very weak and barely palpable. Caffein sodium benzoate and adrenalin chloride were administered to no avail and the child died eight hours after admission to the hospital and within nine hours after ingestion of the kerosene. No laboratory examinations were made.

*Necropsy Findings.* Necropsy was performed eight hours after death.

*Gross Examination.* The body, 73 cm. in length, was that of a well developed, well nourished, white, one-year-old male infant. The pleurae were smooth and moist, and approximately 50 c.c. of clear fluid were present in the left pleural cavity. The lungs were large and heavy and the pleural surfaces were generally dark reddish-blue, but were spotted along the anterior borders by a few small light pink areas and a few slightly raised emphysematous blebs. Sections of the lung revealed moderately wet, uniformly reddened, fairly firm and practically air-free tissue from which a frothy fluid was expressed. A strong odor of kerosene emanated from the pulmonary tissue. The tracheobronchial tree was lined by a pink to slightly red mucosa without ulceration and was filled with frothy pink fluid. Similar fluid filled the nose and mouth.

The lining of the esophagus was smooth, light reddish-blue and without ulceration. The stomach was distended with gas and contained a small amount of tan mucus having a distinct odor of kerosene. The gastric mucosa was without ulceration but that of the fundus was spotted by several small light red areas not more than 2 mm. in diameter. Peyer's patches were moderately prominent in the ileum, pale gray, and speckled with numerous tiny white spots. Tiny 1 mm. mucosal erosions were noted overlying many of the prominent solitary lymph nodules of the colon. Numerous moderately enlarged light tan lymph nodes were contained in the mesentery.

The liver was slightly enlarged and consisted of slightly swollen, slightly congested, light tan tissue mottled with small areas of yellow. An odor of kerosene was detected in the tissue.

The splenic pulp was light red and rather mushy and the gray follicles were prominent.

The cortex of the kidneys was light tan, swollen and slightly congested. The urinary bladder was moderately distended with clear urine which was free from the odor of kerosene. The cortex and medulla of the suprarenal glands were thin but not otherwise remarkable.

There were no abnormalities of the heart other than slight dilatation of the chambers.

Permission was not extended for examination of the central nervous system.

*Microscopic Examination.* Sections representing all lobes of the lungs showed edema, marked hyperemia, some capillary endothelial swelling, focal areas of acute interstitial inflammation, small hemorrhages, and exudate consisting of inflammatory cells in the alveoli (figures 1 and 2). The inflammatory exudate varied somewhat in quantity in various areas but in general consisted of fluid, fibrin, polymorphonuclear leukocytes and mononuclear leukocytes. An occasional foreign body giant cell was present. In some areas the fibrin appeared condensed in a thick red to reddish-blue membrane which was plastered against the alveolar lining (figure 3). Some of the smaller bronchi and bronchioles were partially filled with exudate but presented no evidence of inflammation of the mucosa or supporting tissue. Some, having an intact mucosa, were diffusely infiltrated by inflammatory cells; others showed necrosis of the epithelium with an associated intense inflammatory reaction (figures 1 and 4). Although the alveolar exudate was generalized, it was more pronounced in some of

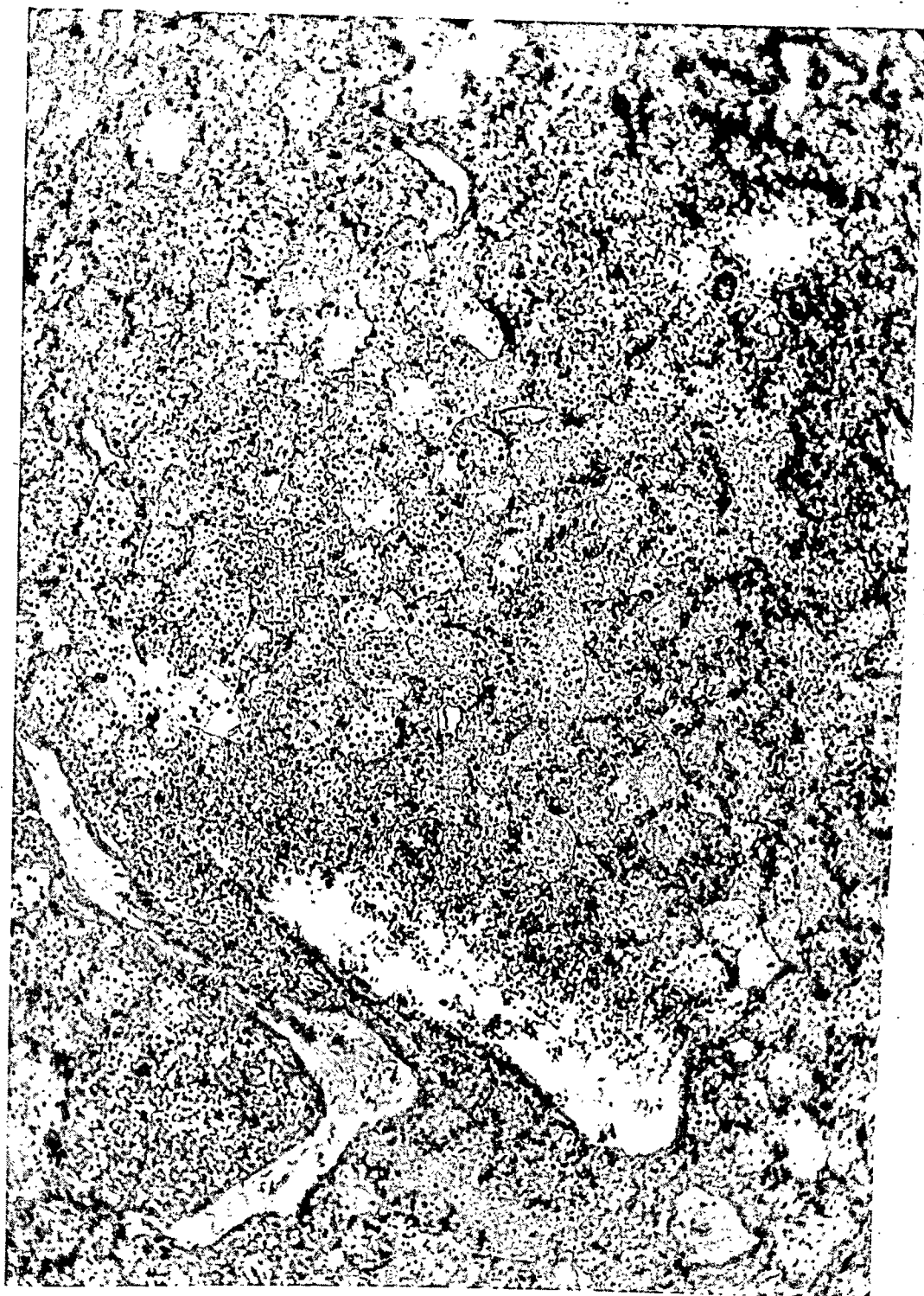


FIG. 1. Section from the lung of a child who died nine hours after swallowing kerosene. Note marked hyperemia, edema and interstitial and alveolar acute inflammatory exudate.

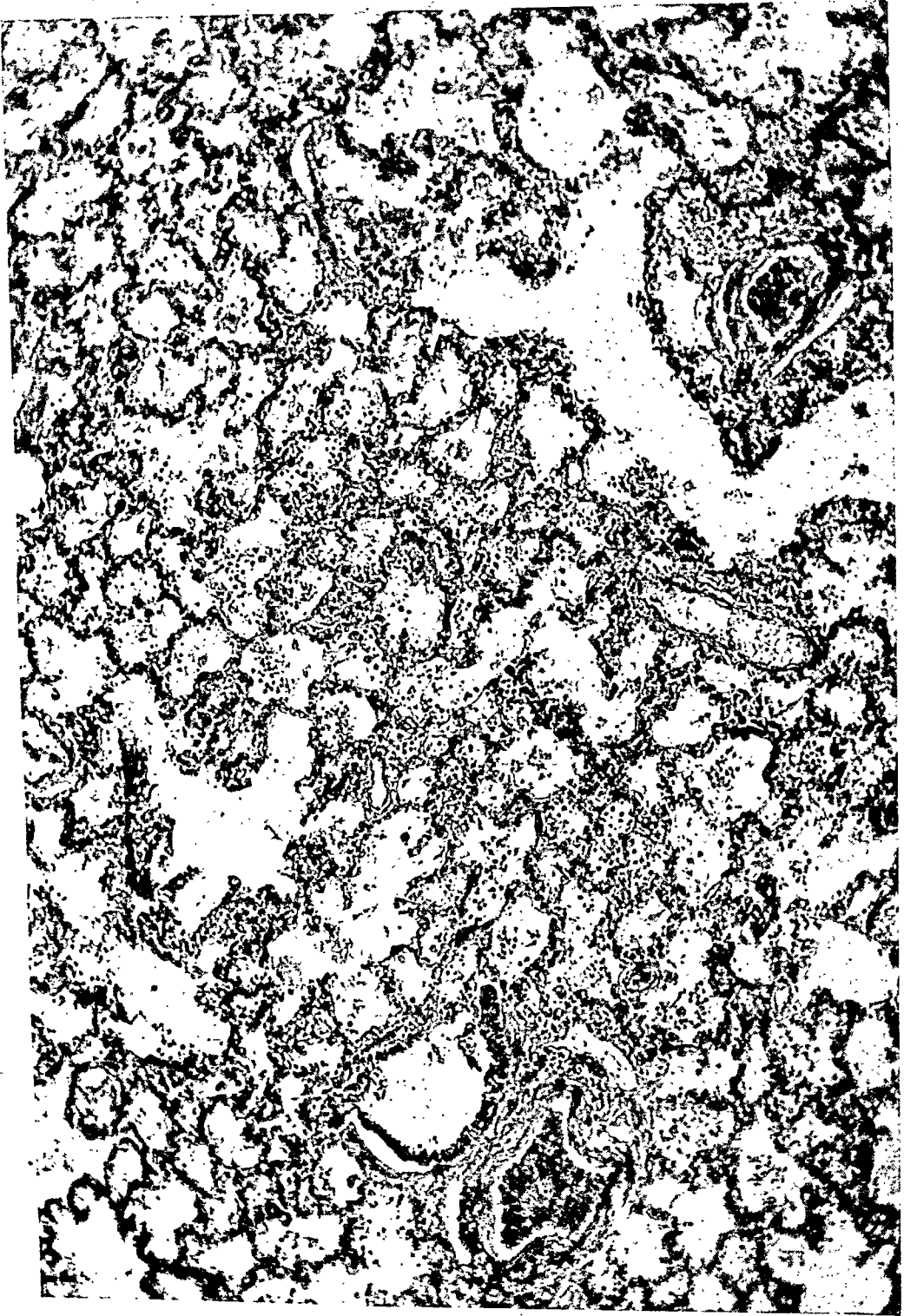


FIG. 2. Section from the lung of a child who died nine hours after swallowing kerosene. Note vascular engorgement and fibrino-cellular exudate in alveoli.



FIG. 3. Section from the lung of a child who died nine hours after swallowing kerosene. Note evidence of vascular and bronchial injury and well defined fibrino-cellular exudate in alveoli.

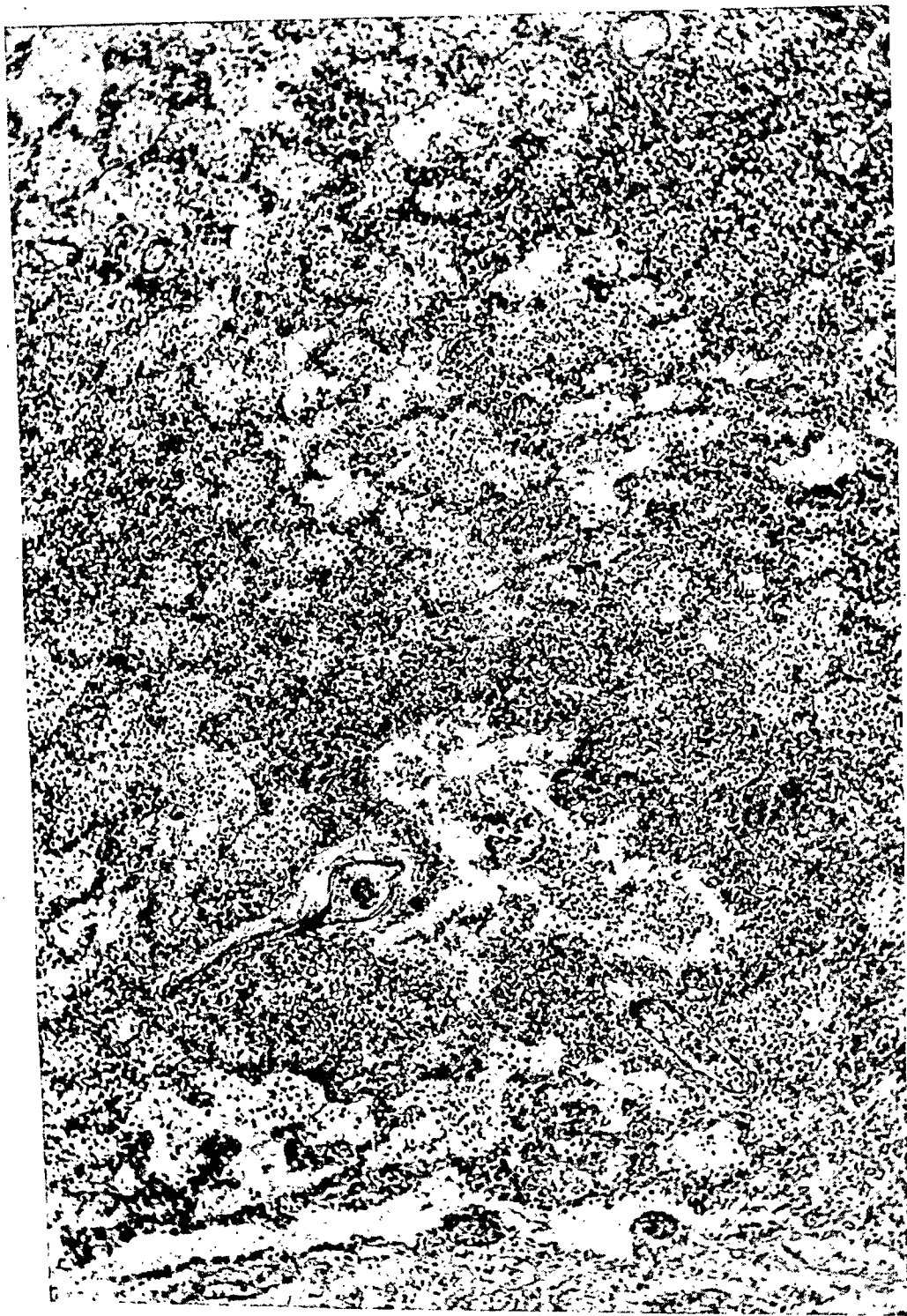


FIG. 4. Section from the lung of a child who died nine hours after swallowing kerosene. Note more intense acute inflammatory reaction in the parenchyma and ulceration of the bronchial wall with loss of epithelium and marked inflammatory cellular infiltration.



the lobules in which the small bronchi and bronchioles presented evidence of ulceration (figures 1 and 4). The epithelium of the trachea and large bronchi was denuded in areas, leaving a bare basement membrane. The lamina propria was moderately congested and contained an occasional petechial hemorrhage. However, there was no evidence of cellular inflammatory reaction. The bronchial lymph nodes were swollen, congested and infiltrated by inflammatory cells, but other lymph nodes throughout the body, notably those in the mesentery, presented only rarefaction of the germinal centers.

The esophagus was essentially normal except for marked congestion of the mucosa and submucosa. The gastric mucosa was intact and, except for moderate congestion, appeared normal. The lymphoid tissue of the small intestine was hyperplastic and slight mononuclear leukocytic infiltration was noted in the tips of some of the villi. There was beginning follicular rarefaction of the solitary lymph nodules of the colon and denudation of the overlying mucosa. Small foci of mononuclear and polymorphonuclear leukocytic exudate were present in the mucosa with extension in a few areas into the submucous layer. In the latter areas the capillaries were congested and collared by leukocytes, and the capillary endothelium was swollen.

In the liver there was congestion of the sinusoids, slight swelling of the Kupffer cells and slight fatty infiltration in the peripheral portions of the lobules. The spleen was congested. Congestion, slight swelling of the epithelial cells of the convoluted tubules, and precipitation of granular material in the convoluted tubules were the principal changes noted in the kidneys. In the heart there was general congestion and small areas were seen in which the muscle fibers were vacuolated and fragmented with loss of cross striations. The bone marrow appeared normal.

*Pathologic Diagnoses.* Acute pulmonary congestion and edema, acute diffuse confluent lobular pneumonia, acute bronchitis, acute bronchial lymphadenitis, slight toxic nephrosis and myocardosis, slight fatty infiltration of the liver, mucosal erosions of the colon, passive congestion of the abdominal viscera.

## DISCUSSION

In the case here described the fatal outcome occurred as the result of rapid absorption of the ingested kerosene from the gastroenteric tract and its passage by way of the blood stream to the organs and tissues of the body, notably to the lungs. Here, as a result of its two-fold action, vascular and parenchymal damage occurred followed by the development of hemorrhagic stasis, edema and diffuse lobular pneumonia. In kerosene poisoning it is undoubtedly true that the bronchi, bronchioles and alveoli contain kerosene both as a result of its hematogenous transfer, and also, in some instances, as a result of aspiration. Pulmonary retention of the kerosene occurs because of its low volatility, for it does not pass from the lungs readily, if at all, in the expired air. As a result of this fact, which has been established experimentally, increased pulmonary ventilation has no beneficial effect other than to prevent anoxia or eliminate it if already present. Thus, the kerosene present in the lungs remains there until removed by other mechanisms and acts as a continuing injurious agent, thereby increasing the degree of inflammatory response and greatly diminishing the likelihood that pulmonary damage will be minimal.

The probability of aspiration of kerosene in regurgitated gastric fluid cannot be denied in most cases of clinical poisoning, but it makes little dif-

ference in the over-all pathologic picture except to add to the damage already present in any serious case of poisoning. Although the development of acute necrotizing lesions in scattered small bronchi is suggestive of direct exposure to the irritant, the presence of these presumably characteristic lesions does not prove conclusively that the irritant has been aspirated, since very similar pathologic changes can be produced in the lungs of experimental animals in which the possibility of aspiration has been completely removed.

### PATHOGENESIS

The pathologic changes caused by kerosene are the result of its irritant action. Locally, whether on the skin or the mucous membranes of the oral cavity, the respiratory or the gastroenteric tract, it is capable of producing severe corrosive lesions accompanied by local exudative inflammatory phenomena conditioned by the physiologic characteristics of the surfaces involved. These lesions may be mild or severe depending on the degree of dilution of the kerosene and the length of time it is permitted to remain in contact with the tissues. Upon its removal healing occurs with complete restoration to normal if the damage has not been too severe. If it has been severe, fibrosis and scarring occur and healing is long delayed and frequently complicated by secondary pyogenic infections.

Following absorption there is evidence of generalized toxemia with depressant effects on the central nervous system as well as on the other organs of the body, notably the liver, kidney and heart muscle. These changes, of course, vary with the degree of exposure and if not too severe may be completely reversible. Vascular damage consisting primarily of cloudy swelling of the intima, media and adventitia, perivascular fluid extravasation and occasional collections of monocytes and lymphocytes in the perivascular spaces, constitutes the essential lesion in all the viscera. Albuminous degeneration and frequent coagulation necrosis occur in the myocardium, liver and kidney. The spleen is acutely congested, contains many phagocytic macrophages and much free hemosiderin. The reticulo-endothelial cells are hyperplastic and the follicles large and active. The most interesting pathologic picture is seen in the lungs in severely poisoned cases. It has long been the accepted opinion that pulmonary changes occur only when kerosene is aspirated,<sup>1, 2, 3, 4, 5, 6</sup> and just recently this opinion has been re-affirmed by Lesser, Weens and McKey<sup>8</sup> following a clinical, roentgenographic and experimental study of the pulmonary manifestations after ingestion and aspiration of kerosene. These authors conclude that "the pulmonary changes are brought about by aspiration of kerosene into the respiratory tract and are not the result of absorption from the gastrointestinal tract with subsequent excretion into the lungs."<sup>8</sup>

It is the primary purpose of this paper to refute these statements and to demonstrate the two-fold nature of the lung injury in kerosene intoxication.

It is not uncommon in toxicologic studies to have pulmonary damage



from excretion of blood-borne materials following their ingestion, cutaneous application, or parenteral injection.<sup>9, 10</sup>

Moon<sup>11</sup> discusses lung injury with the formation of pulmonary edema from increased vascular permeability induced in a variety of ways, principally by injection of foreign protein, histamine, bile salts, and peptone, and by drug poisoning, burns, intestinal obstruction, and by the introduction of muscle substance intraperitoneally. From a review of the experimental work cited below having to do with the toxicology and pathogenesis of kerosene poisoning it becomes apparent that pulmonary damage of this same general type does occur in kerosene intoxication.

### TOXICOLOGY, EXPERIMENTAL PATHOLOGY

*Oral Administration.* In experimental animals large oral doses of kerosene caused increased respiration, hypoglycemia, mild hyperpyrexia (figure 5), progressive muscular weakness and tremor, followed by marked dyspnea,

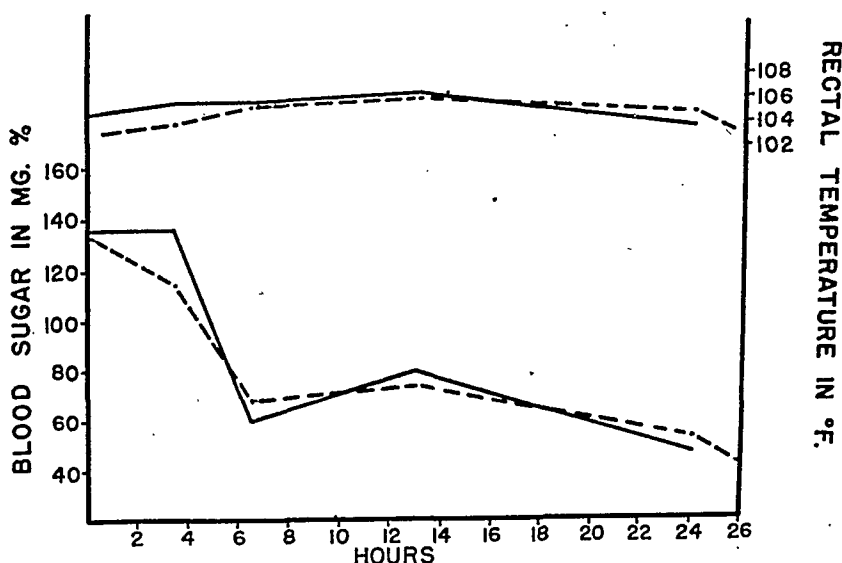


FIG. 5. Effect of a lethal oral dose of kerosene on rectal temperature and blood sugar of two rabbits.

hypopyrexia, and coma frequently resulting in death. Only faint traces of kerosene appear in the exhaled air. The lethal dose ( $LD_{50}$ ) of one sample of kerosene was 28.4 ml. per kilogram for adult rabbits, and 20.4 ml. per kilogram for adult guinea pigs. The compound was even less toxic for adult rats, a dose of 28 ml. per kilogram killing only four of 15 animals. Kerosene obtained from other sources displayed approximately the same degree of toxicity. Tables 1 and 2 summarize the results on these animals.

An experiment was carried out to determine whether or not young animals of other species show the great susceptibility that appears to exist in the case of small children as compared to human adults. The results show

TABLE II  
The Toxicity of One Brand of Kerosene When Administered Orally in One Dose to Adult Rabbits and Guinea Pigs

Number of Animals Employed	Dose ml/kg	Per Cent of Deaths	Time until Death	LD <sub>50</sub>
Rabbits				
10	10.0	0	12 hrs. to 6 days	28.35 ml./kg.
10	16.0	30	2 to 5 days	
10	24.0	40	2 to 10 days	
10	36.0	60		
Guinea Pigs				
10	4.7	10	3 days	20.38 ml./kg.
10	7.0	10	3 days	
10	10.0	10	3 days	
10	16.0	30	1 to 8 hours	
10	24.0	70	1 hr. to 3 days	

that young rats are highly susceptible, the lethal dose for 10-day-old animals being approximately 7 ml. per kilogram (table 3). However, three-week-old rabbits were only little more susceptible than adult rabbits.

*Skin Application.* Three milliliters per kilogram applied to the skin of rabbits daily for six consecutive days, without employing a bandage, caused

TABLE III  
The Toxicity of Orally Administered Kerosene for Rats of Different Ages

Number of Rats Employed	Age	Dose ml/kg	Per Cent of Deaths	Time until Death
15	adult	28	27	1 to 3 days
15	5 weeks	28	66	1 to 4 days
15	10 days	28	100	1 to 3 days
10	10 days	20	100	1 to 3 days
15	10 days	10	100	2 to 4 days
10	10 days	7	50	3 to 7 days
10	10 days	5	40	3 to 7 days

some local loss of hair and scaling and cracking of the epidermis, but did not produce evidence of systemic illness.

*Intravenous and Intraperitoneal injection.* The toxicity of kerosene when injected intravenously into rabbits was determined because of the desirability of using this liquid or one with similar properties, as a solvent for certain solid substances that were to be administered in this fashion. The dose of kerosene was injected into the marginal ear vein at a rate of 0.2 ml. per minute. Signs of poisoning resembled those seen after oral administration. The lethal dose is approximately 0.18 ml. per kilogram (table 4). The intraperitoneal injections were made for the purpose of permitting absorption to

occur over this large surface while preventing all possibility of intrapulmonary aspiration. The lethal dose ( $LD_{50}$ ) following this means of administration was 6.6 ml. per kilogram (table 5).

*Inhalation.* Inhalation exposures were not carried out with animals because the low vapor pressure of kerosene makes poisoning by inhalation unlikely.

TABLE IV  
The Toxicity of Kerosene When Administered Intravenously to Rabbits

Number of Animals Employed	Dose ml/kg	Per Cent of Deaths	Time until Death
4	0.12	0	
4	0.18	50	5 hrs. to 2 days
4	0.28	75	2 hrs. to 3 days
4	0.42	100	1 hr. to 4 days

*Pulmonary Lesions.* The pathologic changes produced in the lungs were of the same general character whether administration of kerosene was by stomach tube or by intraperitoneal injection.

In order to demonstrate the nature of the pulmonary injury, lethal doses of kerosene were injected intraperitoneally in a series of rabbits. These died 7, 9, 11, 13, 24, 30 and 50 hours after treatment. Gross and microscopic examinations were carried out on the lungs of all the animals. The pathologic findings were very similar in all instances except that the lesions were

TABLE V  
The Toxicity of One Brand of Kerosene When Administered Intraperitoneally in One Dose to Adult Rabbits

Number of Animals Employed	Dose ml/kg	Per Cent of Deaths	Time until Death	$LD_{50}$
10	3.2	0		
10	4.7	40	10 to 13 hours	
10	7.0	60	10 to 20 hours	
10	10.0	80	6 to 18 hours	
10	16.0	80	6 to 19 hours	
10	24.0	100	7 to 20 hours	
				6.6 ml./kg.

more advanced in those animals in which a greater time interval had elapsed between treatment and death.

On gross examination the lungs were voluminous. The tense, yellowish pink and dark pinkish red pleural surfaces were moist, smooth and glistening, and the upper lobes were marked posteriorly with dark red subpleural hemorrhagic extravasations. Tremendous emphysema was seen everywhere in the crepitant parenchyma, causing irregularity of the pleural surfaces. On section the cut surfaces were covered with frothy serosanguineous fluid which oozed from the parenchyma, and filled the bronchi and trachea (figure 6).



FIG. 6. Lungs of rabbit which received a lethal oral dose of kerosene demonstrating the pathologic changes as described in the text.

Alteration in the pulmonary circulation with evidence of damage to the vessel walls was the most uniform and consistent finding on microscopic examination. The vessels were acutely congested with engorgement of the venules and capillaries, and frequent hemorrhagic extravasation into the interstitial tissue and alveoli (figure 7). Cloudy swelling occurred in all coats of the vessels, and very frequently there was edema of the adventitia

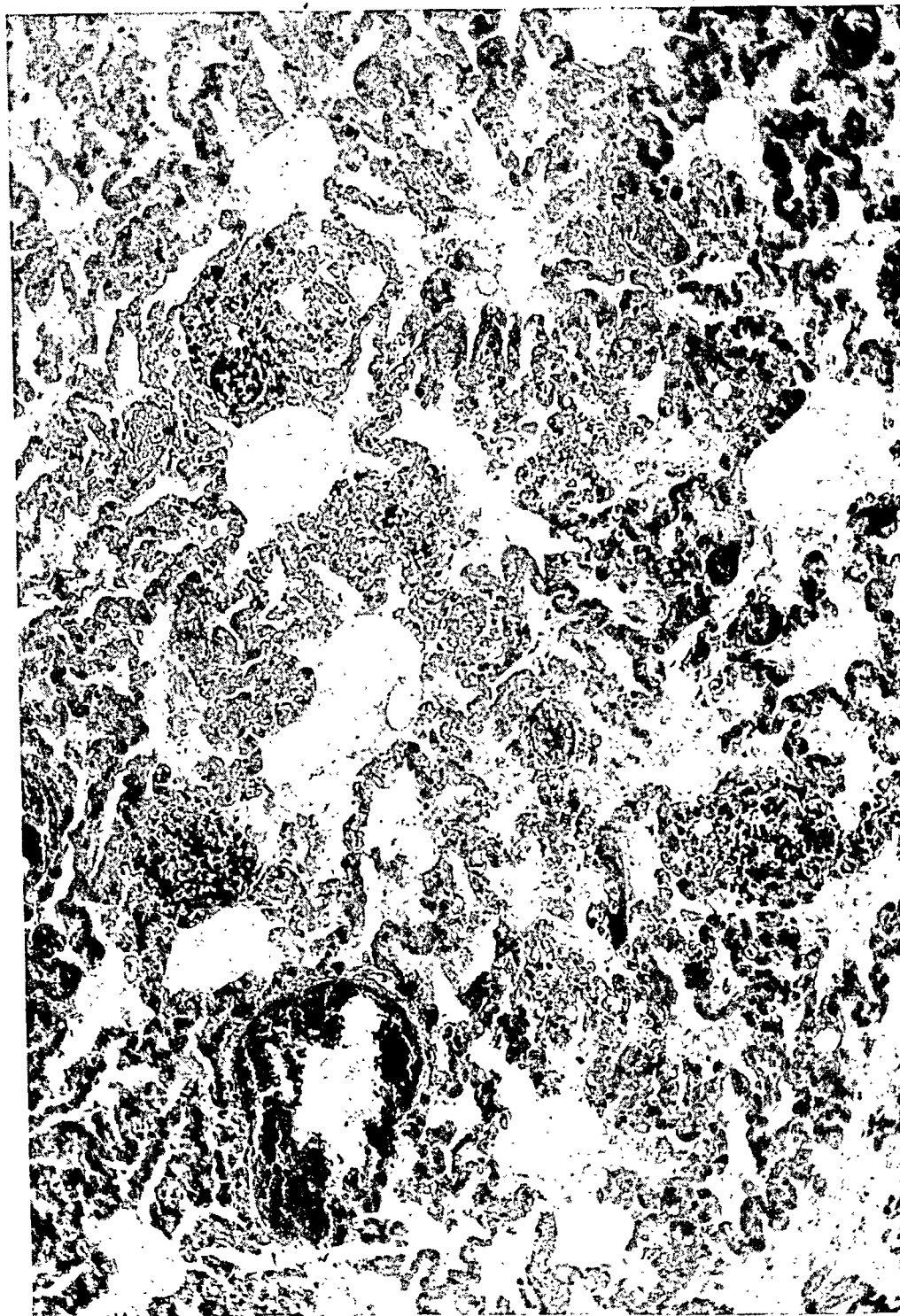


FIG. 7. Section from the lung of a rabbit which died 30 hours after receiving a lethal intraperitoneal dose of kerosene. Note capillary venous engorgement and exudate of some serum and fibrin in the alveolar spaces, as well as occurrence of thrombophlebitis.

with perivascular collections of fluid occasionally containing exudative cells (figure 11). The septa showed evidence of cloudy swelling and were infiltrated with varying numbers of polymorphonuclear leukocytes and fewer monocytes (figure 8). Alveolar edema was not seen earlier than 12 hours after treatment, but from this time on was an important part of the pathologic picture (figure 9). Frank pneumonic exudate was not discovered in any of the sections, although the leukocytic infiltrations were quite extensive in the sections from animals that survived for 12 hours or longer.

The trachea and bronchi of all animals were characteristically altered. The mucosa displayed cloudy swelling and contained numerous goblet cells. Acute congestion was striking in the submucosal tissue especially in the trachea, and the collagenous tissue was swollen and frayed. Varying numbers of monocytes, plasma cells, and lymphocytes were found in collections beneath the mucosa and in the perivascular spaces (figure 10). In the later stages coagulation necrosis and desquamation of the mucosa were frequently seen together with more extensive cellular exudate.

The picture of tracheal and bronchial damage in these animals bore a striking resemblance to that observed in rabbits following inhalation of phosgene and hydrogen chloride.<sup>12</sup> There was also observed the characteristic patchwork distribution of emphysema and atelectasis so frequently seen following pulmonary irritation from inhalation of noxious gases.

*Diagnosis.* Since acute poisoning usually follows the accidental ingestion of kerosene by small children or infants, the container is commonly either in the hands of the victim or lying near by and the sudden attack of coughing or choking directs attention to its content. If the child is unconscious, the odor of kerosene is readily recognized on the breath, vomitus or stomach washings.

Clinical laboratory procedures offer little significant information.<sup>4, 6, 9, 11</sup> If additional confirmation of the presence of shock or impending shock is needed, it may be obtained by a study of the blood picture which ordinarily reveals an elevated white blood count with increase in the percentage of polymorphonuclear leukocytes; and evidence of varying degrees of hemoconcentration as revealed by determinations of the red blood count, hemoglobin, hematocrit and whole blood or plasma protein levels. The urine may contain albumin, casts and red cells and may retain the odor of kerosene for some days. This characteristic odor is also present in the feces.

*Prognosis.* In fatal cases of kerosene poisoning death usually occurs in from two to 20 hours, but may be delayed in rare instances as long as 48 hours. The percentage of fatalities varies in several series of reported cases. Waring<sup>4</sup> reported two deaths in 23 cases; Nunn and Martin<sup>6</sup> six in 65 cases, and Farabaugh<sup>5</sup> five in 120 cases. These figures result in an average fatality of 6.7 per cent.

If gastric lavage is instituted promptly and continued persistently at frequent intervals, most patients will recover rapidly without serious sequelae.

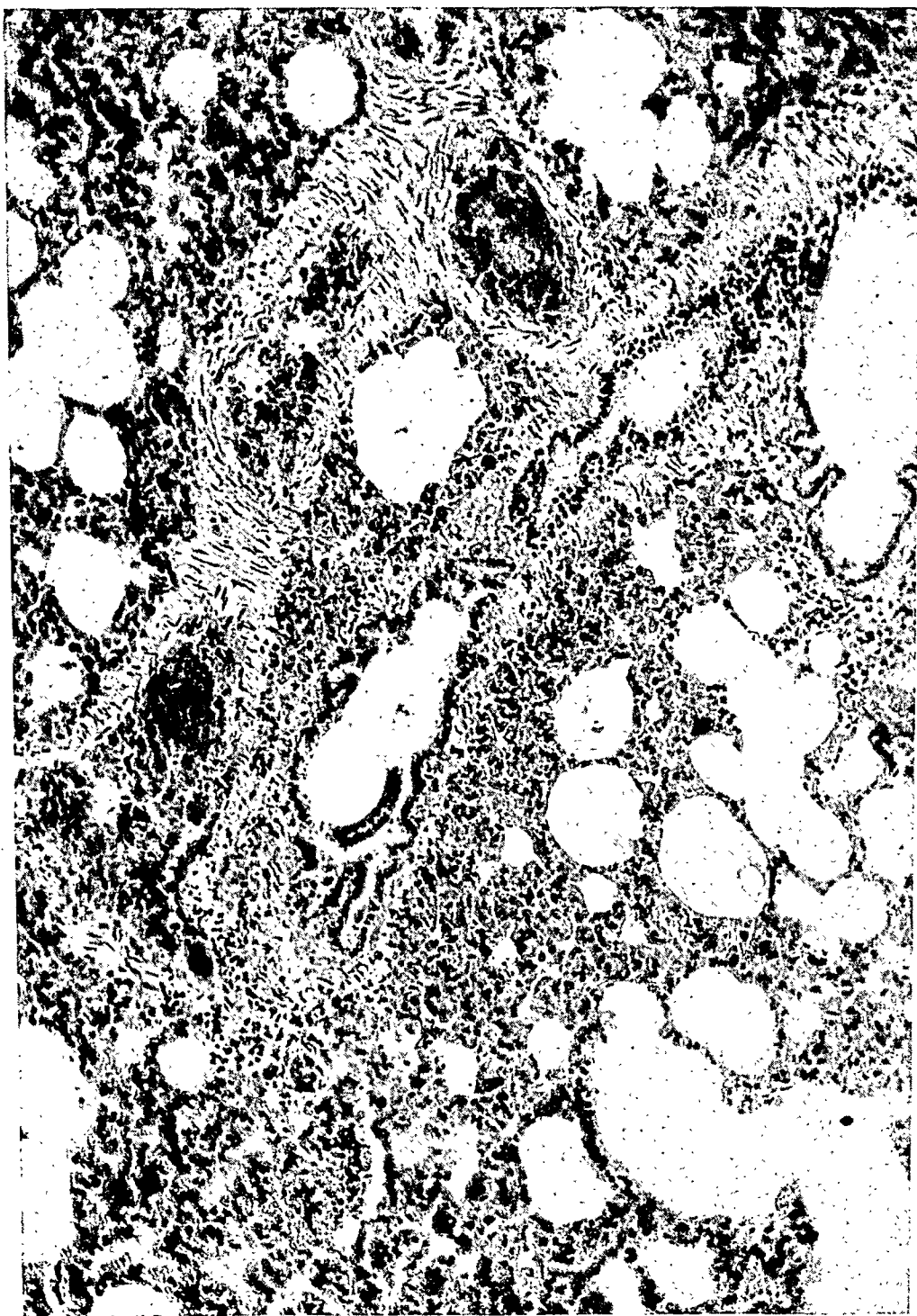


FIG. 8. Section from the lung of a rabbit which died 24 hours after receiving an intraperitoneal injection of kerosene. Note capillary venous engorgement and cellular exudate in septa and peribronchial tissue.

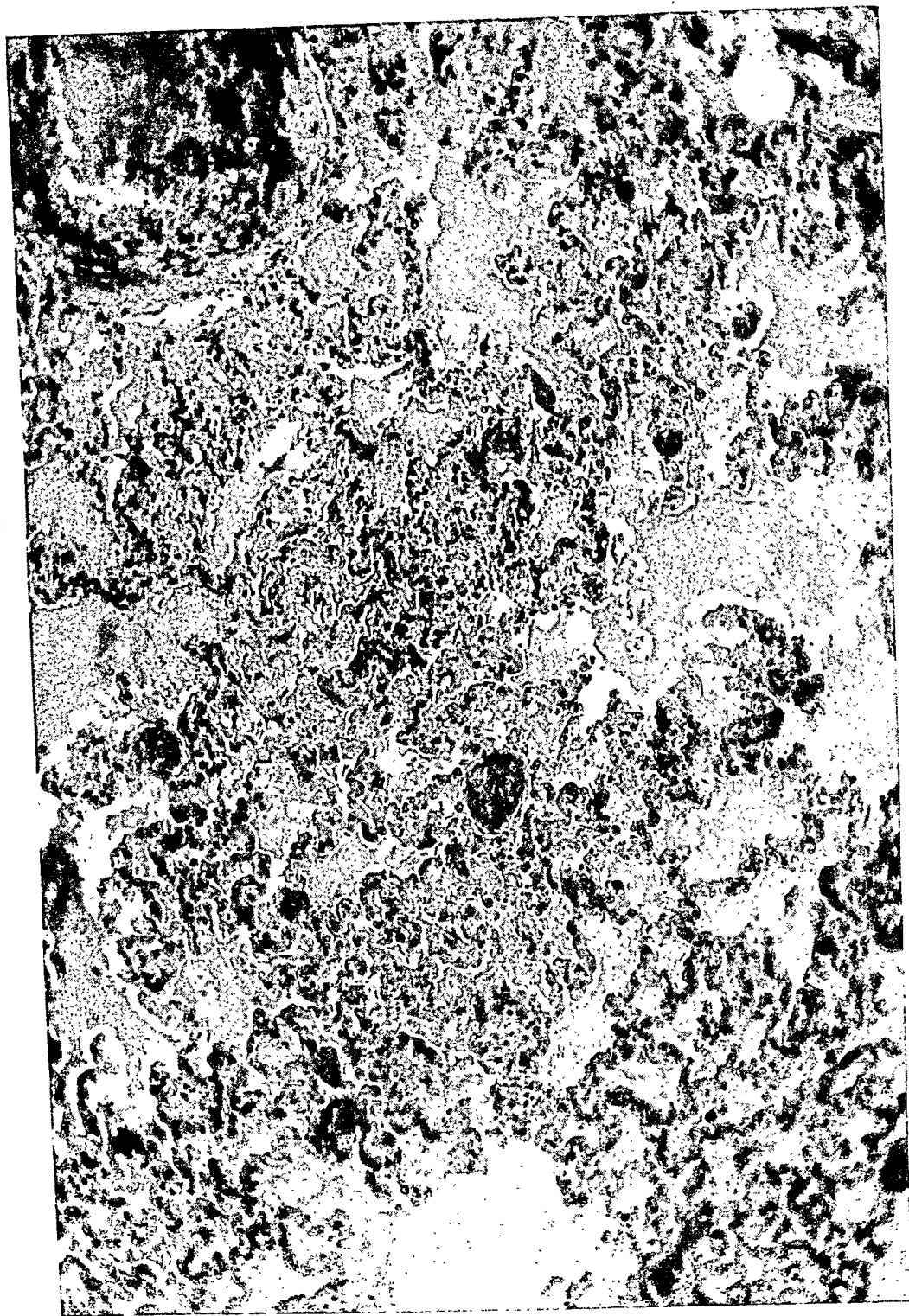


FIG. 9. Section from the lung of a rabbit which died 24 hours after an intraperitoneal injection of kerosene. Note intense alveolar edema and vascular engorgement.





FIG. 10. Section from the trachea of a rabbit receiving a lethal dose of kerosene by intraperitoneal injection with death occurring 11 hours later. Note extreme vascular engorgement and edema of tunica propria with scattered inflammatory cellular infiltration.

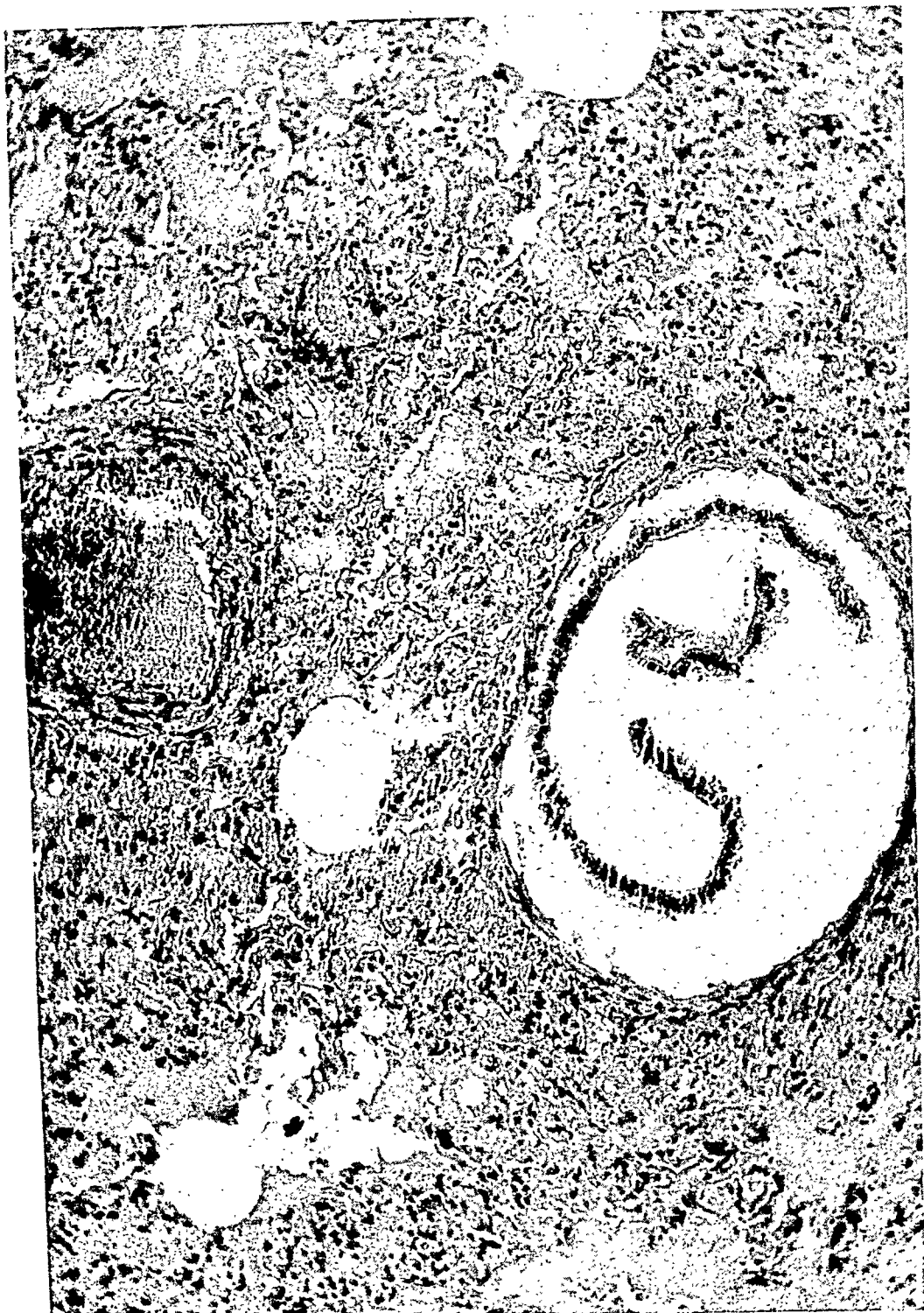


FIG. 11. Section from the lung of a rabbit which died 24 hours after an intraperitoneal injection of kerosene. Note capillary congestion, intense edema, and evidence of vascular and bronchial injury.

If treatment should be delayed or if poisoning is severe, pulmonary irritation offers the greatest hazard. This may be characterized by mild bronchial catarrh or severe acute pulmonary congestion and edema followed by interstitial or alveolar pneumonia. Prognosis is always grave when these severe complications are present. This is due both to the depleting effects of the systemic intoxication induced by kerosene absorption, and to the underlying lung damage and its continuing extension resulting from the presence of kerosene in the lung parenchyma.

Skin lesions caused by local application of kerosene vary in degree from a mild dermatitis to severe third degree burns, the prognosis of which depends on the extent of the skin surface involved.

Lesions produced by intra- or subcutaneous injection of kerosene required several months for healing (Waldstein).

*Therapy.* Among the chief therapeutic objectives should be the dilution of kerosene in the body and its removal as quickly as possible. Both of these conditions are accomplished by immediate and continued gastric lavage using large quantities of warm water or dilute baking-soda solution, and continuing lavage until the odor of kerosene is no longer detected in the washings. These measures also aid in preventing vomiting or regurgitation with aspiration of kerosene. Since the severity of the poisoning depends largely on absorption from the gastroenteric tract, it may be desirable also to give saline cathartics, and high colonic enemas or colon irrigations.

Other therapeutic measures should be supportive and designed to prevent shock, maintain the circulation and respiration, minimize pulmonary edema, and prevent if possible the development of pneumonia. In accordance with the clinical indications, the use of hypertonic glucose solution by intravenous injection may be of value to the heart muscle and liver and may aid as well in the prevention of pulmonary edema. With respect to pulmonary edema, hypodermic medication with atropine and ergotamine may be helpful, and coramine or metrazol helps in maintaining effective cardiorespiratory function. Symptoms and signs of acute anoxia should be immediately combated by the efficient administration of oxygen.

In an attempt to prevent that most serious complication, pneumonia, there can be no serious objection to the use of relatively small doses of one of the sulfa drugs, preferably sulfathiazole, sulfadiazine or sulfamerazine. Ten grains twice daily for adults, with the dosage for children in proportion, should be adequate for this purpose. If pneumonia should develop, the dosage may be adjusted accordingly. In gravely ill patients whole blood and plasma transfusions are of great value.

Since liver damage is not insignificant in kerosene poisoning, measures designed to prevent or minimize this complication should be undertaken. If conditions permit, a diet should be prescribed containing generous amounts of carbohydrate and protein and very little fat, supplemented by cod liver oil

concentrate, ascorbic acid, liver extract, thiamin and Brewer's yeast tablets, as advocated by recent investigators of liver dysfunction.

### SUMMARY

A typical case of fatal kerosene poisoning in a child is reported in considerable detail, together with the gross and microscopic postmortem findings, and the clinical aspects of this type of intoxication are presented extensively.

The lethal oral dose ( $LD_{50}$ ) of a series of different commercial brands of kerosene was found to be approximately 28 ml. per kilogram of body weight for adult rabbits, and 20 ml. per kilogram for adult guinea pigs. By intravenous injection the lethal dose for rabbits was about 0.18 ml. per kilogram and 6.6 ml. per kilogram when administered intraperitoneally. Young rats were found to be more susceptible to the poisonous effects of kerosene than adult animals.

Evidence is presented to support the thesis that in kerosene intoxication pulmonary injury may be sustained from the kerosene carried to the lung by way of the blood stream, as well as from the direct introduction of the fluid into the lungs by aspiration, and that this former route is of great importance in the development of the lung damage which results primarily from vascular injury. Because of the fact that absorption with consequent deleterious systemic effects continues so long as kerosene remains in the gastroenteric tract, every effort should be made to remove it as quickly as possible in treating cases of kerosene poisoning.

### BIBLIOGRAPHY

1. BARBOUR, O.: Kerosene poisoning, *Jr. Am. Med. Assoc.*, 1926, lxxxvii, 488.
2. PRICE, J. P.: Kerosene poisoning in children, *Jr. Am. Med. Assoc.*, 1932, xcix, 214.
3. HIGGINS, J. M.: Rapidly fatal result in a child from ingestion of kerosene, *Pennsylvania Med. Jr.*, 1932-1933, xxxvi, 526.
4. WARING, J. I.: Pneumonia in kerosene poisoning, *Am. Jr. Med. Sci.*, 1933, clxxxv, 325.
5. FARABAUGH, C. L.: Kerosene poisoning, *Minnesota Med.*, 1936, xix, 780.
6. NUNN, J. A., and MARTIN, F. M.: Gasoline and kerosene poisoning, *Jr. Am. Med. Assoc.*, 1936, ciii, 472.
7. OSCHERWITZ, D.: Personal communication.
8. LESSER, L. I., WEENS, H. S., and McKEY, J. D.: Pulmonary manifestations following ingestion of kerosene, *Jr. Pediat.*, 1943, xxiii, 352-364.
9. MACHLE, W., SCOTT, E., and TREON, J.: The metabolism of mononitro paraffins, *Jr. Indust. Hyg. and Toxicol.*, 1942, xxiv, 5-9.
10. TREON, J., CRUTCHFIELD, W. E., and KITZMILLER, K. V.: The physiological response of rabbits to cyclohexane, methylcyclohexane and certain derivatives of these compounds, *Jr. Indust. Hyg. and Toxicol.*, 1943, xxv, 199-214 and 323-347.
11. MOON, VIRGIL H.: Shock and related capillary phenomena, 1938, Oxford University Press, New York.
12. KEHOE, R. A., and KITZMILLER, K. V.: Pulmonary irritants, *Cincinnati Jr. Med.*, 1942, xxiii, 423.

## SYNDROME OF AURICULOVENTRICULAR ACCESSORY PATHWAY \*

By GEORGE KAPLAN, Major, M.C., A.U.S., and THEODORE D. COHN,  
Captain, M.C., A.U.S., *Pittsburgh, California*

THE first record of this abnormality was described by Wilson<sup>1</sup> in 1915, who believed it to be vagal effect. Wedd<sup>2</sup> reported another such case in 1921 and called it "A-V nodal rhythm." Hamburger<sup>3</sup> in 1924 reported four cases of "intraventricular conduction disturbances with unusual clinical features."

Wolff, Parkinson and White<sup>4</sup> were the first to recognize this abnormality as a clinical syndrome. The possibility of an accessory pathway producing this picture was first suggested by Holzmänn and Scherf.<sup>5</sup>

Electrocardiographic tracings have the following characteristic pattern:

- a. Short PR interval.
- b. Prolonged QRS complex with slurring.
- c. Usually oppositely directed T waves.

In a series of 1,672 consecutive electrocardiograms taken at this hospital, this syndrome was observed twice.

### CASE REPORTS

*Case 1.* A white soldier, age 21, with three years and eight months service in the Army, was admitted to the hospital with a history of periodic paroxysms of palpitation of three years' duration. These attacks had a sudden onset at irregular intervals of one to six months and a sudden offset. They were associated with weakness, profuse perspiration, nervousness and pounding in the chest. Between attacks he was able to indulge in excessive physical activity such as football, swimming, and boxing without difficulty. The paroxysms came on at any time and without any relationship to exercise. There was no previous history of rheumatic fever, choréa, or tonsillitis. He had no dyspnea on exertion, except during his attacks of paroxysmal tachycardia. No member of his family had any symptoms which would lead one to suspect the presence of a similar condition.

**Physical Examination.** The patient was a well-developed, male adult, 5 feet 7½ in. tall, weighing 142 pounds, whose blood pressure was 138 mm. Hg systolic and 80 mm. diastolic. Heart: Point of maximum impulse was in the fifth interspace within the midclavicular line. The sounds were of good quality and there were no murmurs. The rhythm was regular sinus and the heart rate 84 per minute. There was a normal cardiac response to exercise, the aortic second sound was greater than the pulmonic second sound. The remainder of the physical examination was normal.

**Laboratory Data.** Urine showed a specific gravity of 1.022, no albumin, no sugar; microscopic examination negative. Blood Count: Hemoglobin 100 per cent, white blood count 7,400, polymorphonuclear neutrophils 74 per cent, lymphocytes 20

\* Received for publication December 14, 1943.

From The Medical Service, Station Hospital, Camp Stoneman, California.

per cent, monocytes 4 per cent, eosinophiles 2 per cent, blood cholesterol was 158 mg. per 100 c.c. of blood; basal metabolic rate minus 5 per cent; sedimentation rate 4 mm. per 60 minutes by the Cutler method; Kahn reaction was negative.

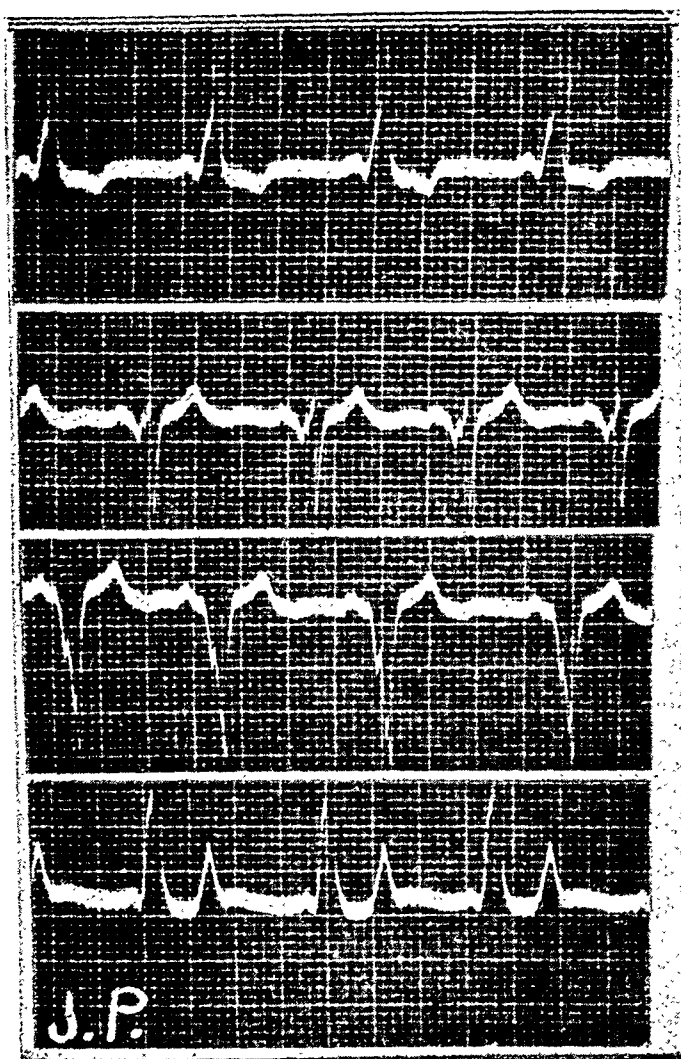


FIG. 1. J. P.

Rate: Auricular 85; ventricular 85.

PR Interval—0.10 Sec.

QRS Complex—0.12 Sec.

Rhythm: Regular Sinus.

P Waves—Upright in I, II and III.

QRS Complexes—Upright, notched and slurred in I; inverted and slurred in II; deeply inverted, slurred and notched in III.

T Waves—Inverted in I; upright in II and III.

Lead IV—Initial Deflection positive. QRS 0.12 sec. T waves upright.

The telecardiogram showed the cardiac silhouette to be well within the limits of normal. The electrocardiogram (figure 1) showed a short PR interval with a long QRS complex and oppositely directed T waves. This patient had practically no disability because of his great capacity for physical work without precipitating an attack.

*Case 2.* A white soldier, age 28, was admitted to the hospital in an acute attack of paroxysmal auricular tachycardia. The patient was dyspneic, apprehensive, with a cold clammy perspiration and an ashen gray pallor to the skin. His heart rate was 210 per minute and the sounds were booming in character. Ocular pressure

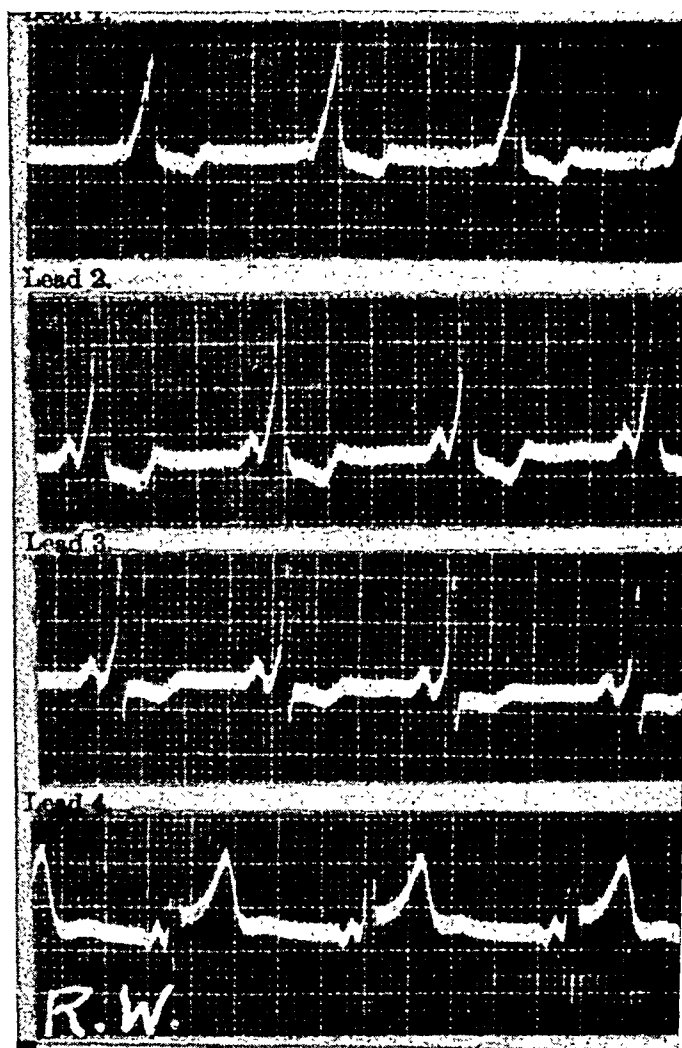


FIG. 2. R. W.

Rate: Auricular 75; ventricular 75.

PR Interval—0.10 Sec.

QRS Complex—0.14 Sec.

Rhythm: Regular Sinus.

P Waves—Upright in I, II and III.

QRS Complex—Upright, notched and slurred in all leads.

T waves—Inverted in I, II and III.

Lead IV—P waves diphasic. Initial deflection positive. QRS 0.14 sec. T waves upright.

caused an immediate cessation of the attack. The patient gave a history of very frequent attacks of "palpitation" for the past five years. These paroxysms were brought on by slight exertion such as a short hike and lasted 30 minutes to 24 hours. An attack could be produced at will. Ocular pressure would invariably stop the attacks. Between the attacks he was free of symptoms and felt well.

Previous history did not reveal rheumatic fever, chorea, or tonsillitis. No member of his family had any symptoms which would lead one to suspect the presence of a similar condition.

**Physical Examination.** The patient was an adult, white male, 5 feet 9 in. tall and weighing 150 pounds. Heart: Point of maximum impulse was in the fifth interspace within the midclavicular line. The rhythm was regular sinus, and the rate 74 per minute. There were no murmurs, and there was a normal cardiac response to exercise. The aortic second sound was greater than the pulmonic second sound. Fluoroscopic examination of the heart in all positions revealed a normal cardiac silhouette and no enlargement of any chamber. The remainder of the physical examination was normal.

**Laboratory Data.** Urine and blood counts were normal; Kahn reaction was negative. Basal metabolic rate minus 14 per cent. The electrocardiogram (figure 2) showed a short PR interval with a long QRS complex and oppositely directed T waves. This patient was definitely disabled because of the ease with which an attack developed.

### DISCUSSION

Aberrant conducting tissue bridging the right auricle and ventricle and known as the right lateral bundle was described by Kent.<sup>6</sup> The most reasonable explanation of this syndrome was advanced by Wolferth and Wood.<sup>7, 8</sup> According to their concept, the impulse originates in the normal pacemaker

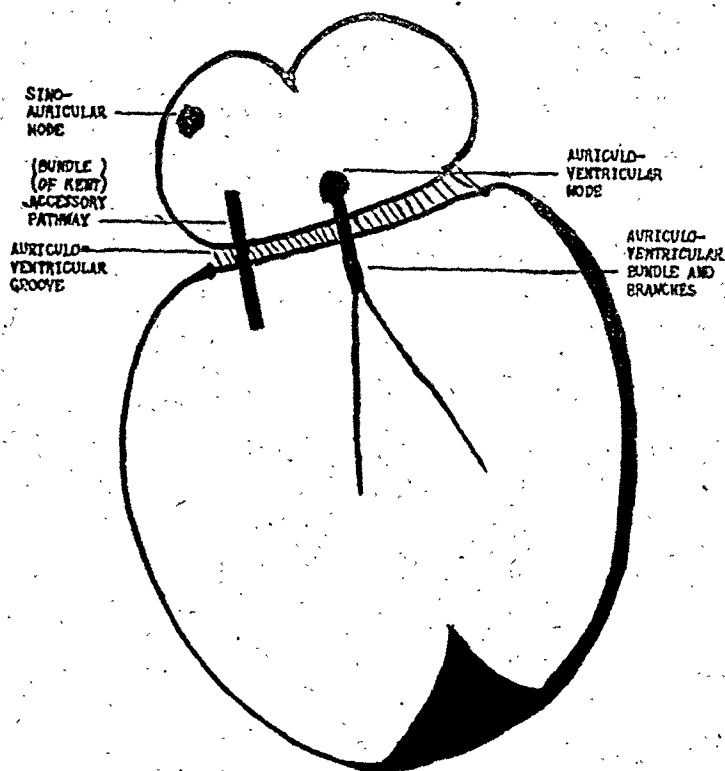


FIG. 3. Schematic drawing showing relation of accessory pathway to the normal conduction system.



(sino-auricular node). It traverses the short distance to the accessory pathway (figure 3), thus causing the short PR interval. By arriving prematurely in the musculature of one ventricle it produces the pattern of a bundle branch block. This explanation is enhanced by the experimental work of Butterworth and Poindexter,<sup>9</sup> who by short-circuiting the impulse in animals, produced a typical electrocardiographic tracing of this syndrome. Wood, Wolferth and Geckeler<sup>10</sup> demonstrated histologically an accessory Bundle of Kent in a case of "Short PR Interval and Long QRS Complex."

The electrocardiogram of the patient in case 2, taken during one of his attacks (figure 4), shows paroxysmal auricular tachycardia with a normal



FIG. 4. Auricular paroxysmal tachycardia rate 210, followed by a long period of asystole and return of normal sinus rhythm via the accessory pathway.

QRS interval of 0.06 second. This is in accord with the concept advanced that the Bundle of Kent is unable to carry the rapid succession of impulses and thus these impulses now traverse the normal cardiac pathways. With eyeball pressure the paroxysm ceased and after a period of asystole the impulse resumed its pathway through the Bundle of Kent. Another strip of electrocardiogram (figure 5<sup>1</sup>) shows the temporary cessation of the

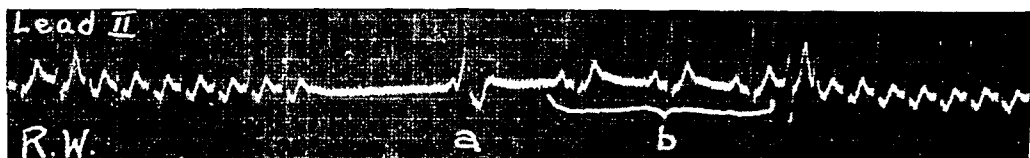


FIG. 5. Paroxysmal auricular tachycardia rate 200, short period of asystole followed by (a) one heart beat through the accessory pathway, then (b) three heart beats via the normal pathway followed by a resumption of the auricular paroxysmal tachycardia.

paroxysm followed by one impulse (a) via the Bundle of Kent and then three successive impulses (b) through the normal conduction pathway of the A. V. node and A. V. bundle, producing a normal PR interval of 0.16 second and a QRS complex of 0.07 second with normally directed T waves. This is followed by a resumption of the paroxysmal auricular tachycardia.

The frequency of paroxysmal auricular tachycardia in this syndrome is explained by retrograde impulses passing from the ventricle through the normal conduction pathway and setting up an ectopic focus in the auricle. Butterworth and Poindexter<sup>9</sup> experimentally produced paroxysmal auricular tachycardia in the cat's heart by retrograde impulses. This concept is also advanced by Wolferth and Wood.<sup>8</sup>

## SUMMARY

1. Two cases of "syndrome of auriculoventricular accessory pathway," occurring in young adults with no clinical cardiac disease, are described.
2. Short PR interval and long QRS complex are the characteristic electrocardiographic findings.
3. The mechanism of this anomaly is discussed.
4. The clinical syndrome is characterized by repeated attacks of paroxysmal auricular tachycardia.

## BIBLIOGRAPHY

1. WILSON, F. N.: A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram, *Arch. Int. Med.*, 1915, xvi, 1008.
2. WEDD, A. M.: Paroxysmal tachycardia with reference to nomotopic tachycardia and the role of the extrinsic cardiac nerve, *Arch. Int. Med.*, 1921, xxvii, 571.
3. HAMBURGER, W. W.: Bundle branch block. Four cases of intraventricular block showing some interesting and unusual clinical features, *Med. Clin. North Am.*, 1924, xiii, 343.
4. WOLFF, L., PARKINSON, J., and WHITE, P. D.: Bundle branch block with short PR interval in healthy young people prone to paroxysmal tachycardia, *Am. Heart Jr.*, 1930, v, 685.
5. HOLZMANN, M., and SCHERF, D.: Ueber Elektrokardiogramme mit verkürzter Vorhofkammerdistanz und positiven P-Zacken, *Ztschr. f. klin. Med.*, 1932, cxxi, 404.
6. KENT, A. F. S.: Some problems in cardiac physiology, *Brit. Med. Jr.*, 1914, ii, 105.
7. WOLFERTH, C. C., and WOOD, F. C.: The mechanism of production of short PR intervals and prolonged QRS complexes in patients with presumably undamaged hearts: hypothesis of an accessory pathway of auriculo-ventricular conduction (Bundle of Kent), *Am. Heart Jr.*, 1933, viii, 297.
8. WOLFERTH, C. C., and WOOD, F. C.: Further observation on the mechanism of the production of a short PR interval in association with prolongation of the QRS complex, *Am. Heart Jr.*, 1941, xxii, 450.
9. BUTTERWORTH, J. S., and POINDEXTER, C. A.: Short PR interval associated with a prolonged QRS complex. A clinical experimental study, *Arch. Int. Med.*, 1942, lxxix, 437.
10. WOOD, F. C., WOLFERTH, C. C., and GECKELER, G. P.: Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short PR interval and prolonged QRS complex, *Am. Heart Jr.*, 1943, xxv, 454.

# THE SYNDROME OF PAROXYSMAL TACHYCARDIA WITH SHORT P-R INTERVAL AND PROLONGED QRS COMPLEX, WITH REPORT OF TWO CASES \*

By JULIUS R. PEARSON, Captain, M.C., A.U.S., F.A.C.P., and ALBERT  
W. WALLACE, Lt. Colonel, M.C., A.U.S., F.A.C.P.

THAT type of paroxysmal tachycardia associated with a short P-R interval and prolonged QRS complex has long provoked the empirical query of the anatomist, physiologist and clinician alike. The comparative paucity of cases and the diversity of conclusions have made for difficulty in final interpretation of this unusual entity. Since Wilson's<sup>1</sup> original description in 1915, much has been added to crystallize it, and each new work presented has stimulated further investigation in an effort to arrive at complete clarification.

In 1893, Kent,<sup>2a, b</sup> working with mammalian hearts, paved the way for the most acceptable theory on the mechanics of this anomaly, by exposing accessory auriculoventricular conduction bundles. In 1913 and 1914, he<sup>2c, d, e, f, g</sup> demonstrated that muscular bridges, connecting the auricles and ventricles, occasionally were to be found in the human heart, which could transmit an impulse independently of the bundle of His. Glomset and Glomset,<sup>3</sup> in their study of mammalian and human hearts, have substantiated the existence of myoneural bridges scattered abundantly over the atria and between the auricles and ventricles in the auriculoventricular groove. Very recently, Wood, Wolferth and Geckeler<sup>4</sup> have examined the heart of an individual who, in life, demonstrated the syndrome of "paroxysmal tachycardia with short P-R interval and prolonged QRS complex," and who died in the last one of these attacks. The heart presented no gross abnormality or evidence of disease, but serial microscopic sections of the auriculoventricular groove in the position at the right lateral border of the heart, as originally demonstrated by Kent, showed muscular bridges connecting the auricle and ventricle. Still further credence to the tenet that these myoneural connections form the pathway for aberrant conduction to produce the abnormal electrocardiograms is supplied in the recent experimental work of Butterworth and Poindexter,<sup>5, 6</sup> who short-circuited the normal auricular conduction system by leading off electrical impulses from the auricle, amplifying them, and using them to stimulate the ventricle. They reported that "the auricular contractions remained perfectly constant, but by turning the amplifier on and off, the abnormal complexes of the short P-R—wide QRS type could be produced at will."

Before any physiological explanation for the syndrome can be studied,

\* Received for publication February 19, 1944.

and because it has been attributed by some to extracardiac factors, it is well to mention briefly some of the responses of the heart to stimulation by its afferent nerves or by various affecting drugs. The cardio-inhibitory vagus nerve is the heart's principal brake; the right vagus mainly subjects the sino-auricular node; the left similarly, but to a lesser degree, controls the auriculo-ventricular node. Each node also receives a partial nerve supply from the opposite side. Right vagal excitation leads to slowing or complete cessation of the auricular beat, with subsequent slowing of the ventricular beat. Stimulation of the left vagus leads to ventricular retardation by depressing auriculoventricular conduction and interfering with the auricular impulses. Both nerves constantly exhibit a certain amount of reflex tone which depends on "afferent impulses flowing to the vagus center along the sinus and aortic nerves."<sup>7</sup> Large doses of atropine frequently paralyze the vagus and eliminate its tonic effect, with resulting escape of the heart at greater speed. The carotid sinus is an important secondary regulator of the heart rate, and pressure upon it produces a stimulating vagal effect and decreases the heart rate. Acetyl-beta-methylcholine chloride causes only slight depression of the sino-auricular node, but acts mainly to depress auricular muscle, the auriculoventricular node and the bundle of His.<sup>8</sup> The supraventricular action of digitalis usually stimulates the vagus and increases the excitability of the carotid sinus. These actions can be negated by atropine. Also, digitalis has a direct action on the conduction bundle, depressing conduction therein, and this action cannot be annulled by atropine. Quinidine is a general protoplasmic poison which prolongs the refractory period of the sino-auricular node and depresses conduction in the auriculoventricular node likewise, thus depressing the speed of the impulse formation and conduction. This slowing is not under vagal influence because it occurs after the administration of atropine, and this drug has no ability to alter the auriculoventricular block caused by the quinidine. All of these observations were pertinent in our experiments to be described below.

The anomalous conduction involves consideration of both extra and intracardiac mechanisms. The most comprehensible, though not unanimously accepted, theory is the one presented by Wolferth and Wood<sup>9</sup> and by Holzmann and Scherf.<sup>10</sup> These workers propounded a short-circuiting of the auriculoventricular node via accessory auriculoventricular bundles to explain the lessened auriculoventricular conduction time. The asynchronous beat of the ventricles and prolonged QRS complex they attributed to the stimulation of first one ventricle, and then to the other via septal-muscular conduction, rather than to the simultaneous conduction through the bundle of His and its ramifications. As to the clinical expression of paroxysmal tachycardia, they assumed a retrograde conduction over the accessory auriculoventricular path, causing a reentry phenomenon in the auricles, and producing to all intents and purposes a circus-like movement at a rapid rate. This prophecy is brought a step closer to acceptability by the discovery of Wood

et al.,<sup>4</sup> in 1943, of such anatomic muscular bridges at the right lateral border of the heart in an individual who, in life, presented the syndrome, thus supplying the keystone to the bridge between the clinical and anatomico-physiological aspects of the problem.

Other theories are worthy of review, though none has stood the test of time nor has had as many adherents as have the champions of the accessory pathway. Wilson<sup>1</sup> concluded that the "vagi were partially responsible for both the change in location of the pacemaker and the abnormality of the ventricular complex." Wolff, Parkinson and White,<sup>11</sup> who clearly established the syndrome, and for whom it was named, first assumed a functional bundle branch block. White has forsaken this assumption for the accessory pathway theory. Parkinson, with Hunter and Papp,<sup>12</sup> later believed that the anomalous beat arose near, but not within, the sinoauricular node, and that the normal ventricular complex was interfered with by a ventricular extrasystole which arose prematurely and low in one bundle branch. Holzmann and Scherf<sup>10</sup> suggested, and Cossio, Berconsky and Kreutzer<sup>13</sup> further hypothesized that the abnormal conduction was the result of excitation of a hyperirritable ventricular focus by the auricular systole. Tung<sup>14</sup> stated that "vagal influence or aberrant distribution of the vagi may be responsible for (the functional) ventricular block in healthy subjects. Release of vagal tone may produce a reversion of the abnormal to the normal mechanism." Recently, Scherf<sup>15</sup> mentioned another possibility in the assumption of a "functional longitudinal dissociation of the auriculoventricular system of the mammalian heart." Katz<sup>16</sup> suggests several possibilities, viz., first that the conduction represents "nodal rhythm or tachycardia with aberrant conduction," the cause "probably similar to that seen in premature auricular systoles except that the aberrant by-pass remains fixed as long as the impulse arises in the A-V node"; second that "a region of block develops in the interventricular septum so that the electrical effect of stimulation of the septum, normally recorded as an isoelectric period, becomes apparent" with the presupposition of "a region with a refractory period longer than normal located near the base of the septum, which alters the electrical resultant; third that "there is a direct path between the sinus node and the ventricle, which permits the impulse in part to pass quickly by the A-V node," "the impulse so conducted shares the control of the ventricles with the impulse transmitted in the usual way." It is apparent in the study of the work of all these men, that there is an element of acceptability in each of their varying theories. To the present, each successive worker on this problem has presented electrocardiographic data to illustrate his interpretations.

In spite of the fact that there is a difference of opinion on the physiological basis for the syndrome, all do agree on its clinical aspects. It may occur at any time from infancy to old age, in either sex, but to date, most of the reports have been in males, and may be associated with an otherwise normal heart or a concomitant cardiovascular or renal lesion. The paroxysm may

come on while the patient is at rest, or after strenuous exercise, or emotion, or may even be an expression of allergy.<sup>17</sup> The palpitation may not make itself evident, the syndrome may be found accidentally by electrocardiogram, or it may be the presenting feature. Usually the tachycardia is of the simple auricular type, but, rarely, it is on a basis of paroxysmal auricular fibrillation or flutter, or paroxysmal ventricular tachycardia.<sup>18, 19</sup> The history is commonly that of many years' duration with remissions. The diagnosis is apparent at a glance at the electrocardiogram when the features of the abnormal conduction are present, namely, a short P-R interval with a prolonged QRS complex which resembles bundle branch block of left, right or intermediate type. In some of the cases, vagal influence is capable of altering this electrocardiogram; in others, no effect is noted. The anomalous conduction may persist independently or in spite of all efforts to convert it to normal, or it may vary unpredictably as a result of spontaneous correction, vagal stimulation or medication with digitalis or quinidine. Previous to the case reported in 1943 by Wood et al.,<sup>4</sup> it was believed that, of itself, the syndrome was probably a benign one, incapable of producing myocardial damage if the bout of tachycardia did not persist too long, and better left without medication, provided the patient was acquainted with all the facts.

Among inductees in the United States Army, tachycardia, and its usual clinical counterpart, palpitation, are frequently presented for study. Two cases of this rare syndrome of paroxysmal tachycardia with short P-R interval and prolonged QRS complex appeared in a representative group of soldiers with cardiac disturbances. In one, the aberrant conduction pattern could be converted to the normal; in the other, the change was never seen spontaneously and could not be effected by any experimentation.

#### CASE REPORTS

*Case 1.* The first patient was a young man of 30 years, who complained of bouts of palpitation occurring since childhood, after exertion, emotion, or often while at rest, and rarely, also when hungry. These bouts were usually self-limited, and he never consulted a physician about them. The present attack had started on the day previous to his coming under the observation of one of us (J. R. P.), following mild exertion and excitement, but ceased on the same night without any medication or interference. His heart rate during the paroxysm was about 260 per minute. On the next day he was asymptomatic, and his electrocardiogram showed upright P waves, P-R 0.08 second, slurring of the ascending limb and notching of the QRS in all limb leads, depressed ST segments, and inverted T waves (figure 1).

Beginning with standard tracings similar to these, the subsequent experiments recorded and discussed here were carried out.

Exercise caused mild increase in rate, but produced no change in the shape or time-relationships of the individual waves. This agrees with the findings of Roberts and Abramson<sup>20</sup> and with those of Fox, Travell and Malofsky,<sup>21</sup> but varies with those of Wolff, Parkinson and White,<sup>11</sup> who were able to abolish abnormal complexes by exercise and cause reversion to normal conduction, and with those of Bishop,<sup>22</sup> who was able to cause fleeting changes resembling the normal after exercise.

Tracings were then made with the body in various positions and under the in-

fluence of high and of low oxygen tensions, all without resulting alteration in the contour of the waves or the conduction pattern.

Indirect vagal stimulation by carotid pressure did not change the electrocardiogram with the exception of a mild slowing of the rate. This was more noticeable by pressure on the right than on the left carotid, and this finding is comprehensible since the right vagus controls the sinoauricular node. As has been pointed out, the left vagus controls the auriculoventricular node, which is not traversed by the anomalous impulse. (Carotid pressure likewise had little effect on the normal conduction pattern later obtained by quinidinization.) The inability to convert the abnormal

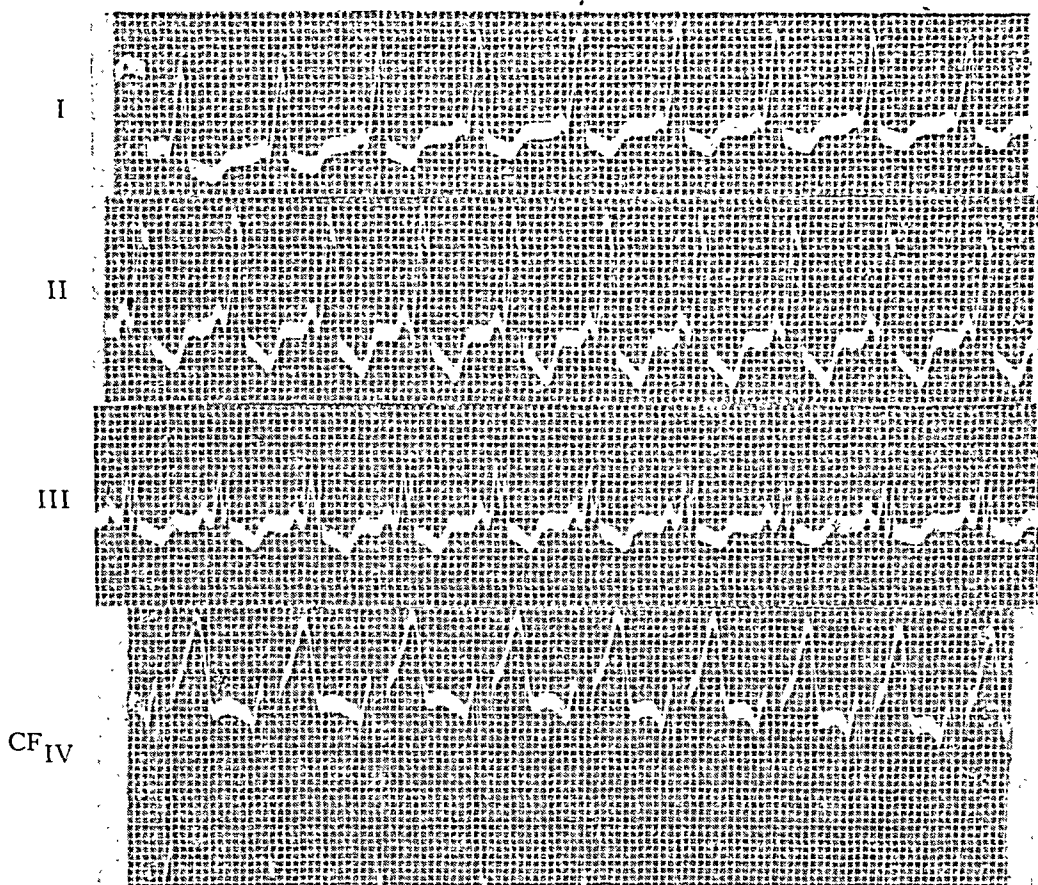


FIG. 1. 4/7/43. Tracings made on the day after the bout of paroxysmal tachycardia. No medication had been given.

graph to the normal by vagal stimulation thus differs from the findings of Wedd<sup>23</sup> and of Sigler,<sup>24</sup> and corroborates those of Roberts and Abramson and more recently of Fox et al.

Vagal paralysis by atropine had no effect on the curves and merely caused an increase in the heart's speed. This agrees with the reports of Roberts and Abramson, Bishop, and Butterworth and Poindexter, but differs from that of Fox et al., who produced shortening of the QRS complex with the increased speed, and from that of Wilson, and Wolff et al., and Tung. Wilson originally stated that the "abnormal rhythm, when spontaneously present, could be converted into the normal rhythm by the administration of atropine in doses sufficient to paralyze the vagi."

In the series of experiments with drugs having effect on the myocardium, the conduction system and the sympathetic-parasympathetic nervous systems, none caused any change from abnormal to normal conduction except quinidine sulfate. Prostigmine had no effect after atropine. Adrenalin, theophylline, ergot and morphine each

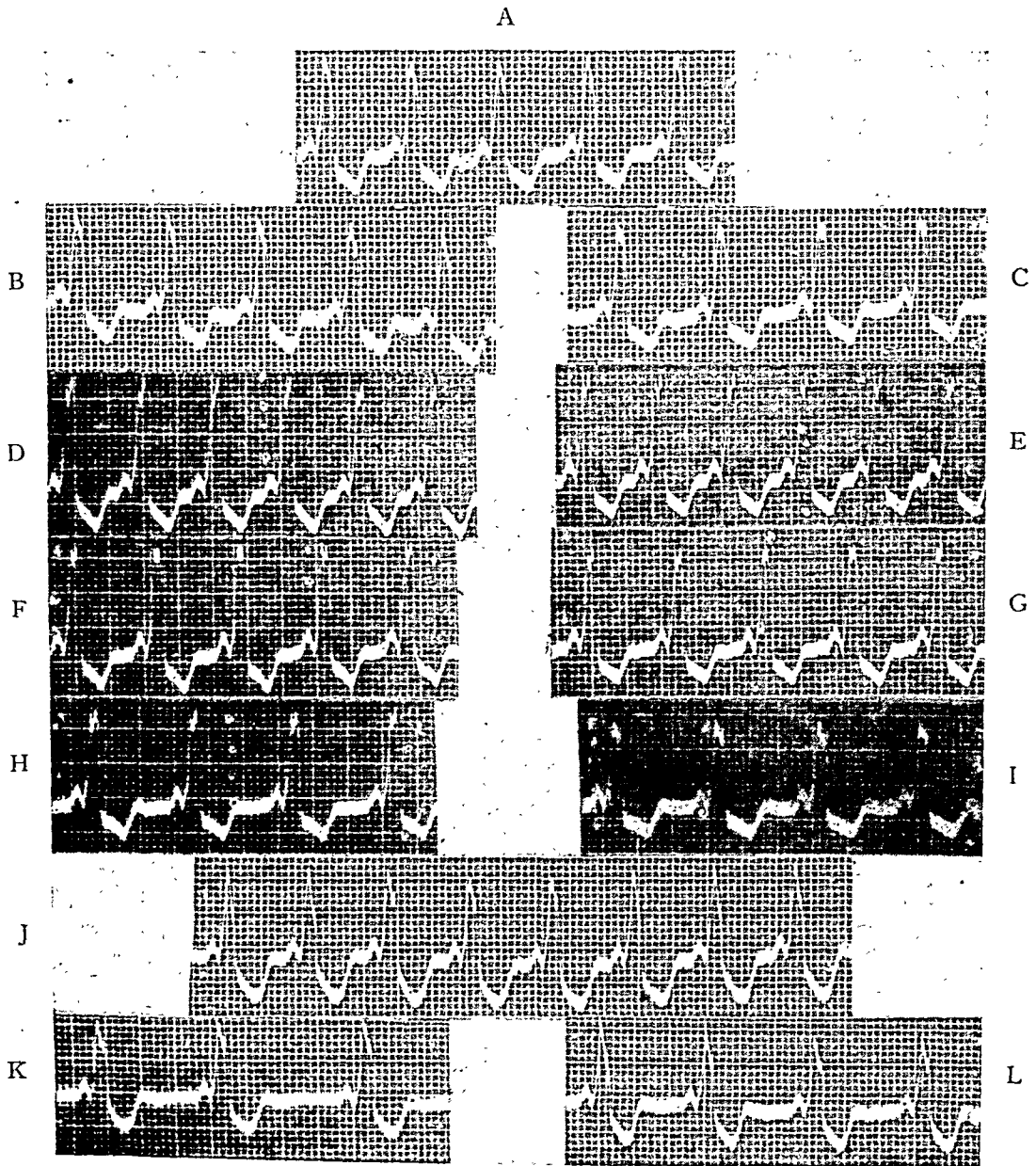


FIG. 2. (A) After exercise. (B) Left carotid pressure. (C) Right carotid pressure. (D) After atropine. (E) After prostigmine. (F) After theophylline. (G) After adrenalin. (H) After ergot. (I) After morphine. (J) After amyl nitrite. (K) High oxygen tension. (L) Low oxygen tension. (All tracings are made in Lead II.)

slowed the heart rate moderately but did not alter the complexes in time-ratios or contours. Amyl nitrite caused only an increase in rate. Fox et al. have recently demonstrated a flexibility of the QRS under the influence of these drugs which was not confirmed here (figure 2, composite).



Tracings made under the influence of a full clinical dosage of digitalis (18 c.u. in six days) showed practically no change in the complexes except for marked slowing of the rate to 50 per minute, a sinus arrhythmia, somewhat lessened voltage, slight slurring of the ascending limb of R and lowering of the initiation of its descending limb in Lead II, rounding of the ST segments, and in Lead III, one complex which is reminiscent of those in Lead II (figure 3). This was a typical physiological-electrocardiographic demonstration of the action of digitalis in full dosage, showing a restraining effect on the sinoauricular node, depression of conduction through the auricular muscle, and direct action on the conduction bundle. Scherf and Schonbrunner<sup>25</sup> found in one case that digitalis in large doses abolished the abnormal QRS complexes for three weeks, and suggested that the accessory pathway was more susceptible to digitalis than was the bundle of His. Apparently the findings in our ex-

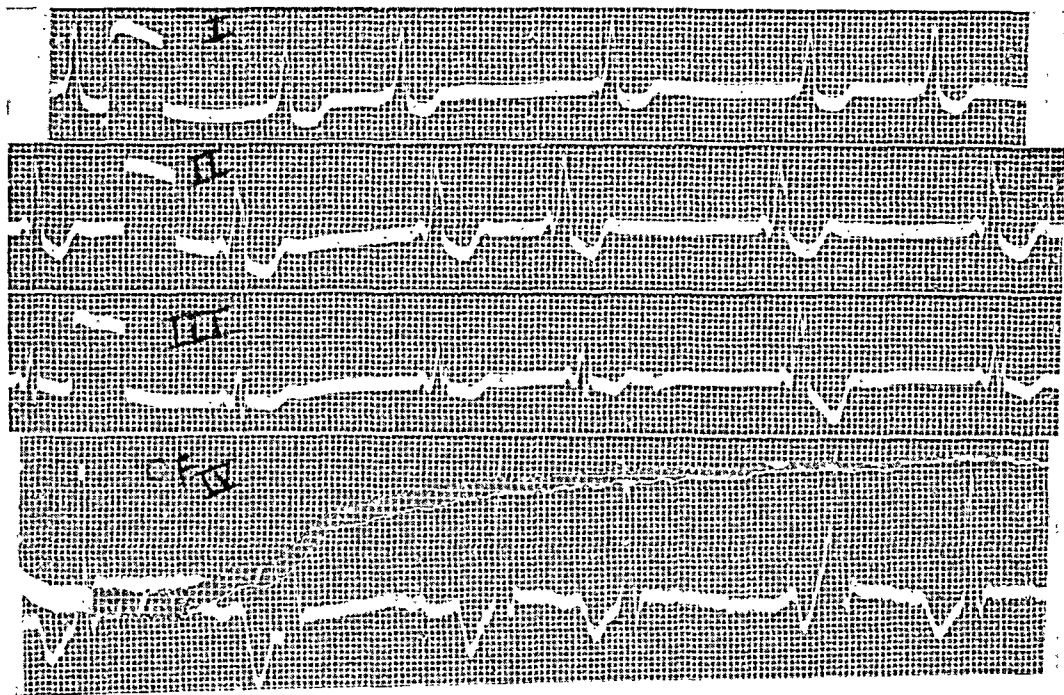


FIG. 3. After 18 cat units of digitalis had been given in a period of six days.

periment show the opposite, since the bundle of His was affected, whereas the accessory pathway was untouched.

During the entire time, physical examination revealed an inconstant impurity of the first heart sound over the mitral area, heard best during the periods of digitalization and quinidization. The blood pressure remained fairly steadily near the level found on the days after admission to the hospital in spite of all manoeuvres. Fluoroscopically and teleoroentgenographically, the heart was well within normal limits of size and contour. There was also present a spina bifida occulta of the first sacral segment. Other than this, no abnormalities or congenital anomalies were discernible on physical or clinical examination. Circulation times, measured by the calcium gluconate method, were determined while the heart was in abnormal conduction and then in normal conduction by means of quinidine. In the former, the arm to tongue time was 15 seconds; in the latter, 11 seconds.

When the heart had reasonably emerged from the influence of digitalis (18 days after the last dose), the patient was given quinidine sulfate, after eliminating possible

sensitivity, in four repeated doses of gr.v each. One hour later his electrocardiogram showed changes to the normal type of conduction (figure 4). The tracings showed: upright P waves in limb leads; P-R 0.16 second; QRS 0.06 second; deep S in Lead I, small S in Lead II; small Q in Lead III; ST practically isoelectric; T diphasic in Lead III, otherwise upright. At this time the total length of the P-T was about 0.48 second whereas on the first day the abnormal conduction measured about 0.44 second. The normal conduction was permitted to revert to the abnormal on the same day

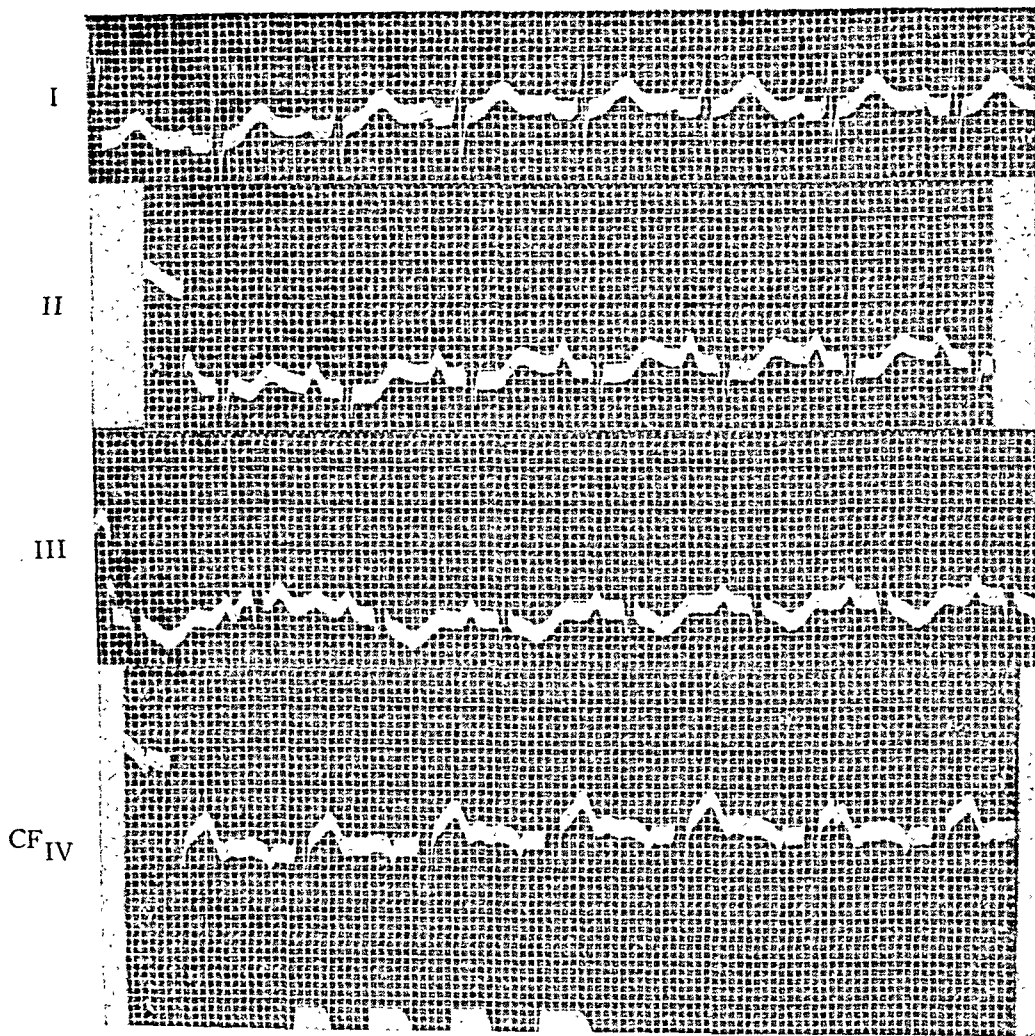


FIG. 4. After quinidine sulfate, given in gr. v doses every two hours for four doses. The tracings were made one hour after the fourth dose.

merely by discontinuing the quinidine, and at a later date reconverted to normal by repeating the experiment. Again indirect vagal stimulation by carotid pressure, and vagal atonia by atropinization were produced, but no change to the abnormal type of conduction occurred, and no alteration of this picture's time-ratios or contours was observed. The conversion of the unusual tracings to the normal type by quinidine agrees with the work of Roberts and Abramson,<sup>20</sup> Wolferth and Wood,<sup>9</sup> and Levine and Beeson.<sup>10</sup> The first authors reasoned that the lower level of development of the anomalous conduction tissue made it more easily responsive to depressants like

quinidine than was the bundle of His. Wolferth and Wood, however, argued that the quinidine also caused reduction of myocardial irritability in general, and that "this therapeutic result cannot be used as an argument in favor of the hypothesis of an accessory pathway of conduction." This denial cannot be accepted without reserve in the face of the failure to convert the abnormal conduction to the normal after our experiment with acetyl-beta-methylcholine chloride and atropine followed by quinidine, which will be discussed below.

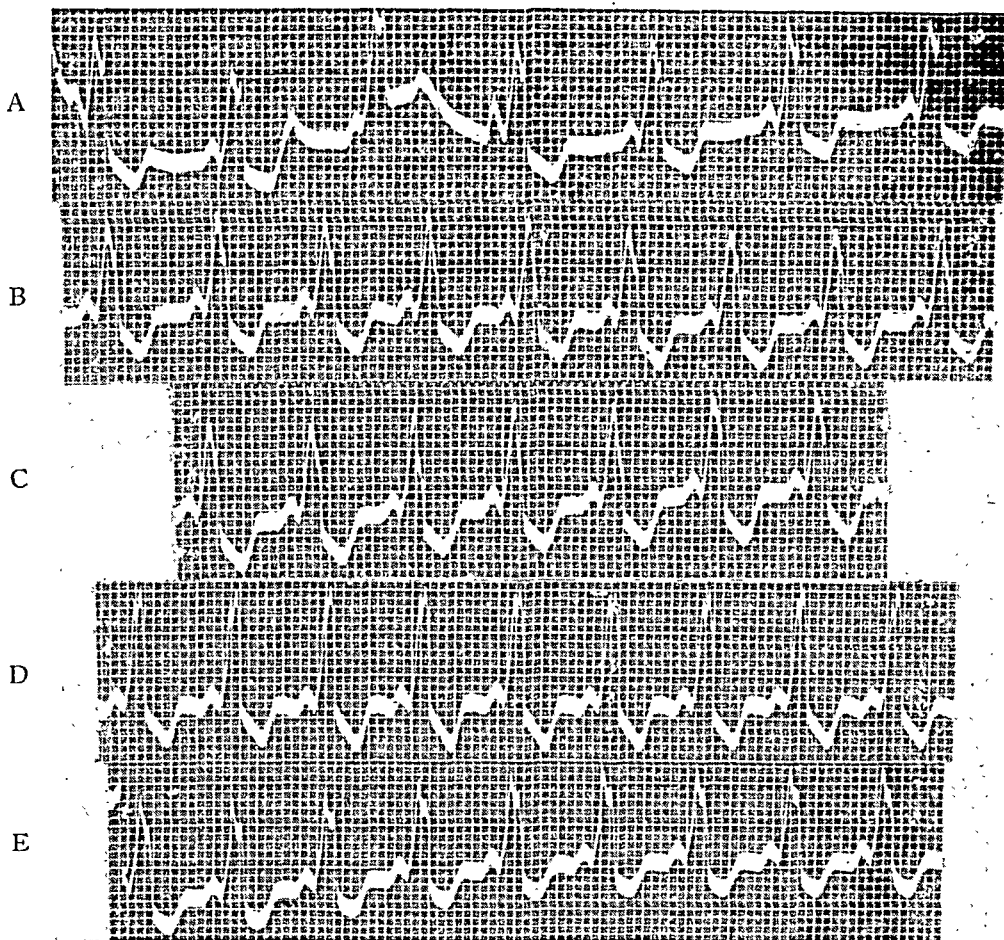


FIG. 5. Lead II in each tracing. (A) Standard. (B) 1 minute after mechohyl subcutaneously. (C) 5 minutes after mechohyl. (D) 2 minutes after atropine intravenously. (E) 20 minutes after atropine.

After a four day rest period to eliminate quinidine from his body, a standard set of tracings was made. The PR measured 0.08 second, the QRS, 0.12 second. His blood pressure was 110 mm. Hg systolic and 60 mm. diastolic, and his heart rate, 90 per minute. Immediately thereafter, he was given 0.2 gm. acetyl-beta-methylcholine chloride subcutaneously. There was full clinical response, but with moderate tachycardia (120 per minute) instead of the expected slowing, and but little change in blood pressure (100 mm. Hg systolic and 50 mm. diastolic). The entire picture of flushing, lacrimation, salivation, profuse perspiration and respiratory bubbling was terminated by the intravenous injection of 0.0012 gm. atropine sulfate. His blood pressure rose at once to 170 mm. Hg systolic and 100 mm. diastolic, and his heart rate

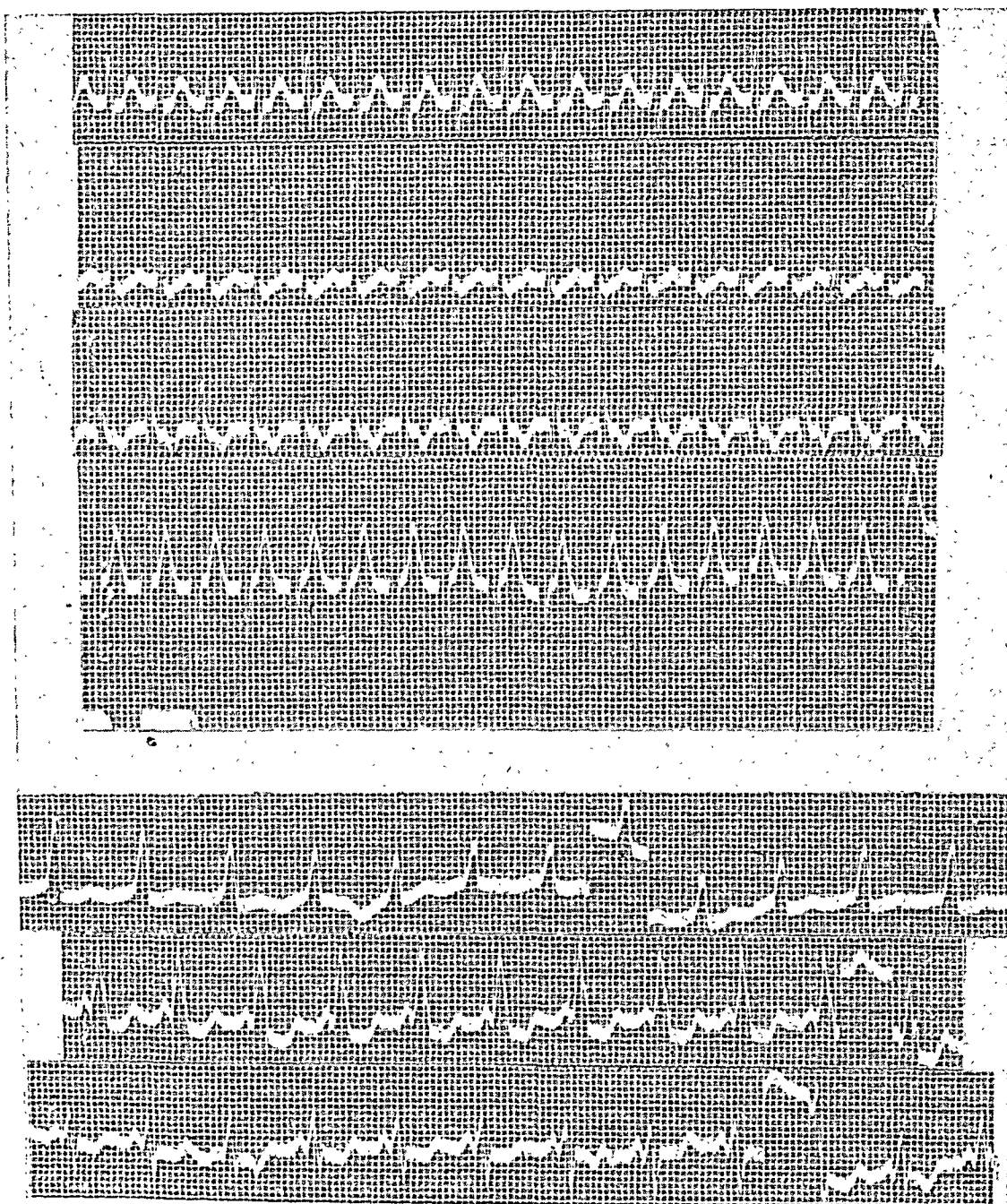


FIG. 6. During attack of paroxysmal tachycardia (above) and immediately after its conclusion (below).

to 130 per minute. The only alteration in the graphs resulting from the mecholyl was a slight depression of the descending limb of the R wave and a similar depression of the ST segment. The atropine, however, banished this effect, and 20 minutes after the atropine had been given, the tracings did not differ from the standard except for slight rounding of the ST segment. The PR measured 0.08 second and the QRS, 0.10 second; the PT was 0.04 second shorter than the original standard (figure 5).

This experiment, with exactly the same end results, was repeated one month later. The blood pressure rose from 120 mm. Hg systolic and 80 mm. diastolic to 170 mm. Hg systolic and 100 mm. diastolic, and the electrocardiographic measurements duplicated those mentioned previously.

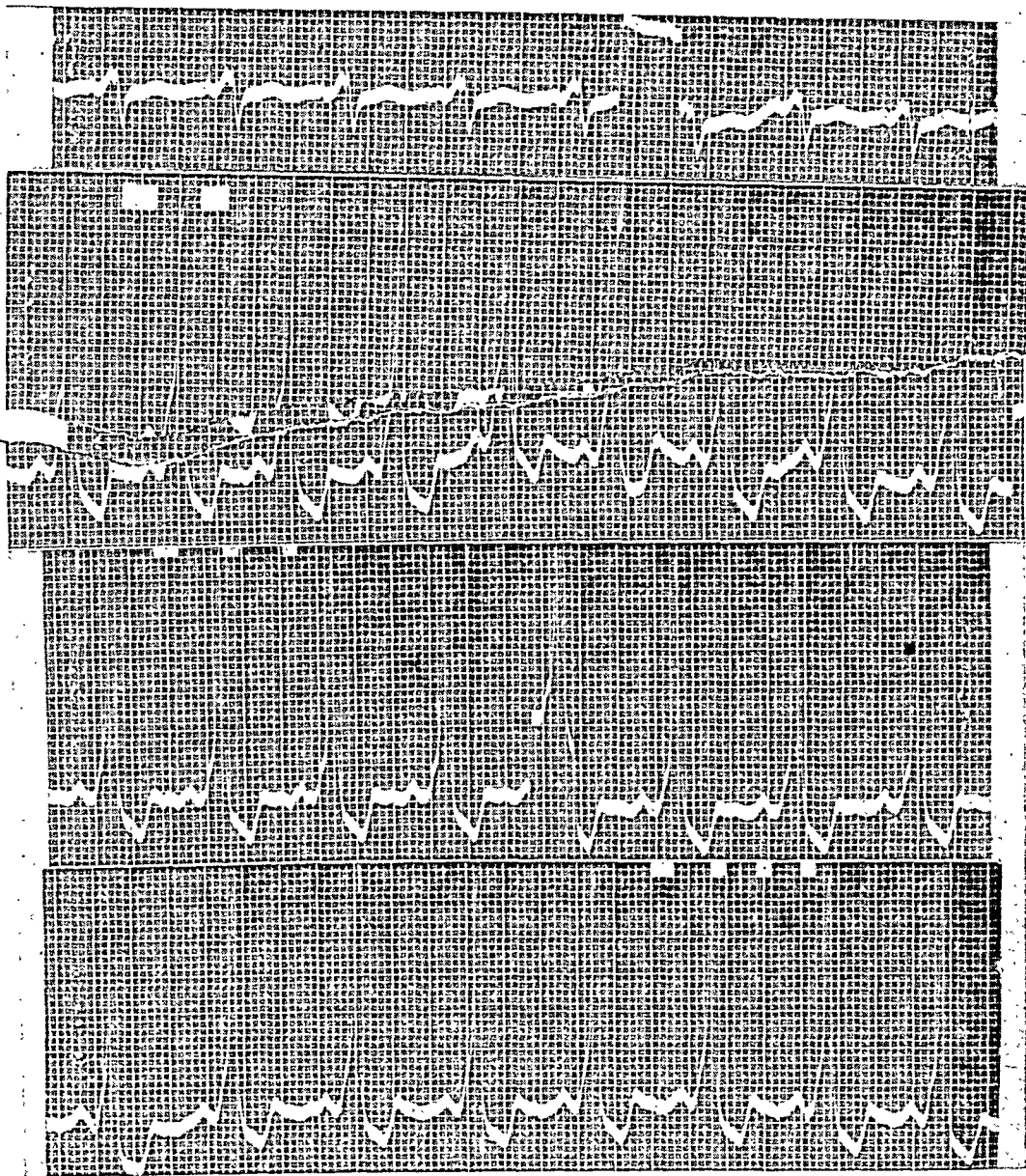


FIG. 7. Case 2. Tracings of the aberrant conduction pattern, from which there was no variation under any circumstance.

Immediately following this experiment the first time, an attempt was made to quinidinize the patient in the same simple manner as previously, with divided doses by mouth. This time no conversion to the normal type of conduction occurred, and the only change consisted of a lengthening of the PT to 0.52 second, a mild slowing of the rate, and a minute depression of the descending limb of the R wave and the ST



segment. He was again rested and reestablished to normal conduction on the next day with the simple method of quinidinization. On subsequent days, quinidine was given at longer intervals, but apparently this longer spacing could not convert the aberrant conduction to normal, for he was never found in the latter on such a régime. After the second mecholyl-atropine experiment, quinidine was able to cause conversion to the normal conduction pattern. Just before he was discharged from the hospital, the patient had a bout of tachycardia which terminated spontaneously before any more than a four-lead electrocardiogram could be made. See figure 6 for tracings made during and immediately after this attack.

*Case 2.* The second patient was 26 years of age. He stated that he had begun to have bouts of palpitation, associated with shakiness and dizziness, five years before he came under our observation. These attacks usually occurred in the latter part of the day, when he was tired from his work, and were usually relieved by merely resting for about 20 minutes. They continued intermittently for about one year and disappeared thereafter under a régime of lighter work and long rest periods. However, following induction into the Army and resumption of a more strenuous physical program, the bouts returned during exertion and were also associated with considerable precordial pain. Physical and roentgenographic examinations disclosed no abnormalities. His blood pressure was 130 mm. Hg systolic and 76 mm. diastolic; sedimentation rate 11 mm. and 5 mm. in one hour; circulation time 12 seconds; serologic reactions, blood count and urinalysis normal.

His electrocardiogram showed the typical characteristics of the short P-R interval and prolonged QRS complex. The P waves were upright; P-R 0.10 second; QRS 0.16 second; deep S in Lead I; tall, slurred, upright complex in Leads II and III; depressed ST-T segments in all. Carotid pressure, alternately over both sides, produced no change in the tracings. The atropine, quinidine-atropine, and mecholyl-atropine experiments previously described in case 1 were repeated without effecting any marked change in the characters. Quinidine caused temporary increase in slurring, slight rounding of the ST-T segments, and slight slowing in the rate. Mecholyl caused increase in the rate, but this slowed after atropine. Digitalis in huge doses (53 c.u. in nine days) had little effect clinically, and did nothing to the tracings except to depress further and round the ST-T segments. In short, the existing time ratios of the P-R and QRS characters remained unaltered throughout all manipulations.

#### COMMENT

Wolferth and Wood object to the Wolff, Parkinson and White hypothesis of bundle branch block because "patients who have both normal and abnormal complexes are likely to show the same interval between the beginning of the P wave and the end of the QRS complex in both." Roberts and Abramson also agree with this objection since, in their case, the P-S distance in both abnormal and normal tracings was practically the same—0.274 to 0.279 second. The findings in our work also deny the bundle branch block theory, but on different grounds. When a bundle branch block exists, its P-S interval is longer than the normal. The P-S distance in the abnormal conduction pathway in the first case showed a time interval of 0.20 second, and in the normal (under influence of quinidine) of 0.24 second, at practically all speeds. During the paroxysm of supraventricular tachycardia, however, the P-S was 0.08 second, and quickly thereafter returned to 0.20 second with reversion to aberrant conduction and cessation of the paroxysm. In

the second case, the P-S interval remained at 0.26 second under all circumstances.

The Hunter-Papp-Parkinson hypothesis of partial dislocation of the pacemaker from the sinoauricular node, and interference with the normal ventricular complex by a premature beat arising low in one bundle branch is very unpredictable. It is dependent upon a similarly abnormal expectation that the two impulses constantly maintain a sequential time relationship with each other, for short or long periods of time, at every possible total speed, and during any other mechanism of the heart. However, anything which would change the regular firing of the impulse from the auricle would not necessarily interfere with the lower impulse, and there should then appear an imprint of the latter at a varying relationship with the former. Each total complex should, therefore, differ in contour and time relationship. This is not borne out, however, by a perusal of our record made under the influence of full dosage of digitalis, in which an arrhythmia was produced, but in each beat the QRS complex follows sequentially the P wave without any variation. Even a dissimilar beat in Lead III shows the same relationship of waves and times as in the remainder of the tracing. Again, under the influence of various other drugs used, or mechanical means tried, to alter the complexes, the same P:QRS appears. In the works of Roberts and Abramson and of Moïa and Inchauspe,<sup>26</sup> and very recently in that of Clagett,<sup>17</sup> there are tracings in which the patients, without any treatment, showed a spontaneous transition from the abnormal complex to alternate groupings of abnormal and normal complexes. Here, too, there was no disturbance of the P-QRS relationships in alternate complexes or in sequential complexes—a feat truly remarkable if this were left to the chance mechanism suggested by Hunter et al.

Against the theory of functional bundle branch block with auriculoventricular nodal rhythm is (a) the maintenance rate of the heart in our patients, which is about double that usually found in this type of retrograde conduction, (b) the complete independence of these hearts of vagus stimulation and inhibition, and (c) the freedom from digitalis influence of the time intervals of the individual elements of the electrocardiograms. These facts reason against any possibility of hyperirritability of the junctional tissue which would be expected in auriculoventricular nodal rhythm, and point rather to a state in which the tissue and node are more refractory to stimulation than usual.

As for the hypothesis of Holzmänn and Scherf, later reiterated by Cossio et al., that the auricular systole mechanically excited a hyperirritable focus in the ventricle, the best answer is forwarded first by Wolferth and Wood,<sup>8</sup> who point out that such a phenomenon "has never been observed in patients with heart block, and never been achieved experimentally, nor ever observed or produced in animals." No further conflict on this point can arise following the animal experimental work of Butterworth and Poindexter, who

could cause the inscription of tracings of the short P-R interval and prolonged QRS complex by applying the input electrode at any point in the auricle and the output electrode at any site in the ventricle. According to this, all points in the ventricle were hyperirritable, which would, therefore, negate the hypothesis.

Several observers have shown tracings in which the character of the P wave is altered in certain complexes, notably before the aberrant ones and before occasional extrasystoles. In addition, there has appeared a change in the P-R time interval. The explanation seems to be readily supplied by the anatomical evidence that the sinoauricular node is made up of an extensive network of interlacing fibers, from any part of which the impulse may originate, the closer to the ventricle, the shorter the P-R interval and the more apt is the P wave to vary from the normal. In their animal experiments, Butterworth and Poindexter could regulate the length of their P-R intervals by lessening or increasing the distance of the input electrode of their amplifier from the region of the sinoauricular node. Furthermore, with the recent demonstration of Wood et al., of at least three muscular bridges connecting the auricle and ventricle in the heart of a patient who had the abnormal conduction pattern, it is very possible that all were capable of conduction, and from varying distances from the sinoauricular node. This would very easily account for minor changes in the P-R interval and P wave in other cases. In our tracings made when the patient was thoroughly digitalized (figure 3), there appears in Lead III one abnormal beat simulating the character of those found in Lead II, which probably represents an impulse from another focus, and may, therefore, be interpreted broadly as an extrasystolic auricular beat. This shows a P wave just like the others, P-R, QRS, and a total P-T interval of exactly the same length in each beat. In this example, it is possible that the digitalis prevented the shortening of the P-R interval.

Concerning the ventricular portion of the tracings, the most frequently reported type is that resembling left bundle branch block, although graphs of right bundle branch block, as in our second case, and of intermediate stages of partial intraventricular block have also been demonstrated. Pardee<sup>27</sup> raised an element of doubt as to the existence of an auriculoventricular accessory pathway which could cause the inscription of an electrocardiogram of the type of the right bundle branch block. Wolferth and Wood considered the right ventricle as the site for the completion of the short-circuiting pathway, later revised their opinion and concluded that the accessory conduction tract led directly to the left ventricle, and recently examined a heart in which the connections were as they originally stated. However, the experimental findings with amplification of Butterworth and Poindexter seem to answer these equivocations, for they reported that with the input electrode in the region of the sinoauricular node and the output electrode on the right ventricle, curves of left axis deviation were inscribed (this is in accord with the



electrocardiographic findings in the above mentioned heart), and that with the output electrode on the left ventricle, tracings of right axis deviation were obtained. It is reasonable to expect that the bizarre conduction pattern may establish a fixed pathway across any of the myoneural bridges connecting the auricles and ventricles in the auriculoventricular groove that were found by Kent, and by Glomset and Glomset, and by Wood et al. anatomically.

To this point, all the theories except the one presented by Wolferth and Wood have been briefly discussed. Very little can be culled from the writings antagonistic to the accessory pathway hypothesis, and all objections that have been raised to it are overcome in an analysis of such contrary evidence. Pardee's question as to the existence of a pathway to produce a configuration of right bundle branch block is anatomically answered by the findings of Glomset and Glomset, and by Wood et al., and experimentally, by the amplifier work of Butterworth and Poindexter. This similarly eliminates Tung's objections as to extra-auriculoventricular connections and impulse transmission. Hunter, Papp and Parkinson denied its accuracy, partly, on grounds of inconstancy of the contour of the P wave and variation in that of the major complex. Wolferth and Wood have held, however, that the contour of the P wave is constant. Butterworth and Poindexter have experimentally found it to be constant. In any event, it is not actually important in interpretation of the mechanism of ventricular stimulation. Any variation may further be interpreted as effects of the manoeuvres and drugs given to study the reactions of the stimulation and inhibition of the sympathetics and parasympathetics. In our own study the reactions are similar, and this deduction is likewise borne out. The argument that Hunter et al. presented regarding the fact that only two types of QRS should be present if the accessory pathway theory is correct—one for the aberrant conduction and one for the normal conduction, with no intermediate types—has been similarly answered by Wolferth and Wood as representing degrees of inverse variation in conductivity of the accessory tract and the bundle of His, and a shifting pacemaker from a focus in proximity to the sinoauricular node to one at a lower level, nearer the auriculoventricular node. Our tracings made during and immediately after a paroxysmal attack show this shift in Lead III, as the heart was apparently recovering from the tachycardia and reassuming the "normal" aberrant pathway of conduction. However, there was an omission of the intermediary type of the QRS in the sudden change from abnormal conduction to the normal under the influence of quinidine.

On the cause of the tachycardia, an interesting theory was first presented by deBoer<sup>28</sup> in 1923. He suggested the existence of an auriculoventricular bundle which formed one link in a path over which a continuous movement of the impulse proceeded from auricle, to bundle of His, to ventricle, to bundle of Kent, to auricle, etc. The hypothesis of Wolferth and Wood is similar, and Butterworth and Poindexter provide the experimental evidence

in their ability to produce a supraventricular tachycardia of about 300 beats per minute by reversing their amplified current from ventricle to auricle in the abnormal pathway. As to the occasional occurrence of paroxysmal ventricular tachycardia, Wood et al.<sup>4</sup> point out that "a premature reentry into ventricular tissue might initiate an abnormality of the ventricular mechanism, just as premature reentry into auricular tissue might initiate an abnormality of the auricular mechanism."

From the foregoing, it becomes evident that recent anatomic and experimental evidences have been presented in favor of a theory of conduction which is primitive in nature and philogenetically understandable. Its common electrocardiographic expression goes hand in hand with the equal rarity of occurrence of the clinical syndrome. The proposition of the existence of an accessory pathway has stood the critical investigation of interested workers longer than the other varying theories have, and at present, it is the most inclusive and comprehensible one of all. Further examination of the postmortem findings of these interesting rare anomalies should define, with exactness, the clinical interpretations that have tested the imagination of the reporters of this syndrome.

#### CONCLUSIONS

Anatomical, physiological and experimental evidence is accumulating in favor of the accessory pathway hypothesis as an explanation of the syndrome of benign paroxysmal tachycardia with short PR interval and prolonged QRS complex.

Some variations from previous findings are presented in the cases studied that differ with or lend credence to the accumulated evidence.

Vagal stimulation and inhibition were ineffectual in abolishing the abnormal conduction pattern, as were also all drugs used to stimulate or depress the sympathetic and parasympathetic nervous systems in general.

In one case quinidine sulfate was the only drug which was able to cause abrupt change from abnormal to normal conduction, and on one occasion this too failed, following the subjection of the patient to acetyl-beta-methylcholine chloride and atropine.

Digitalis was incapable of converting the impulse from the unusual pathway to the normal even in full doses.

Maintenance of normal conduction by means of quinidine is unnecessary in these cases unless other factors involving organic or functional changes in the heart occur as the result of continued tachycardia.

#### BIBLIOGRAPHY

1. WILSON, F. N.: The production of auriculoventricular rhythm in man after administration of atropine, Arch. Int. Med., 1915, xvi, 989. *Ibid.*: A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram, Arch. Int. Med., 1915, xvi, 1008.

2. KENT, A. F. S.: (a) Proceedings of Physiol. Soc., November 12, 1892, Jr. Physiol., 1893, xiv, 23.  
 (b) Researches on the structure and function of the mammalian heart, Jr. Physiol., 1893, xiv, 233.  
 (c) Observations on the auriculoventricular junction of the mammalian heart, Quart. Jr. Exper. Physiol., 1913-1914, vii, 193.  
 (d) The structure of the cardiac tissues at the auriculo-ventricular junction, Jr. Physiol., 1913-1914, xlvii, 17.  
 (e) The right lateral auriculo-ventricular junction of the heart, Jr. Physiol., 1914, xlviii, 22.  
 (f) A conducting path between the right auricle and the external wall of the right ventricle in the heart of a mammal, Jr. Physiol., 1914, xlviii, 57.  
 (g) Illustrations of the right lateral auriculo-ventricular junction in the heart, Jr. Physiol., 1914, xlviii, 63.
3. GLOMSET, D. J., and GLOMSET, A. T. A.: A morphologic study of the cardiac conduction system in ungulates, dog and man, Am. Heart Jr., 1940, xx, 389.
4. WOOD, F. C., WOLFERTH, C. C., and GECKELER, G. D.: Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short P-R interval and prolonged QRS complex, Am. Heart Jr., 1943, xxv, 454.
5. BUTTERWORTH, J. S.: The experimental production of the syndrome of apparent bundle branch block with short P-R interval, Jr. Clin. Invest., 1941, xx, 458.
6. BUTTERWORTH, J. S., and POINDEXTER, C. A.: Short P-R interval associated with a prolonged QRS complex, Arch. Int. Med., 1942, lxxix, 437.
7. BEST, C. H., and TAYLOR, N. B.: The physiological basis of medical practice, 1943, Williams and Wilkins Co., Baltimore, p. 346.
8. GOODMAN, L., and GILMAN, A.: The pharmacological basis of therapeutics, 1941, Macmillan Co., New York, p. 356.
9. WOLFERTH, C. C., and WOOD, F. C.: The mechanism of production of short PR intervals and prolonged QRS complexes in patients with presumably undamaged hearts: hypothesis of an accessory pathway of AV conduction (Bundle of Kent), Am. Heart Jr., 1933, viii, 297. *Ibid.*: Further observations on the mechanism of the production of a short PR interval in association with prolongation of the QRS complex, Am. Heart Jr., 1941, xxii, 450.
10. HOLZMANN, M., and SCHERF, D.: Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, Ztschr. f. klin. Med., 1932, cxxi, 404.
11. WOLFF, L., PARKINSON, J., and WHITE, P. D.: Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia, Am. Heart Jr., 1930, v, 685.
12. HUNTER, A., PAPP, C., and PARKINSON, J.: The syndrome of short P-R interval, apparent bundle branch block, and associated paroxysmal tachycardia, Brit. Heart Jr., 1940, ii, 107.
13. COSSIO, P., BERCONSKY, I., and KREUTZER, A.: P-R acortado con QRS ancho y mellado (análisis de las 34 observaciones de la literatura médica, incluyendo 7 observaciones personales), Rev. argent. de cardiología, 1936, ii, 411.
14. TUNG, C. L.: Functional bundle branch block, Am. Heart Jr., 1936, xi, 89.
15. SCHERF, D.: An experimental study of reciprocating rhythm, Arch. Int. Med., 1941, lxxvii, 372.
16. KATZ, L. N.: Electrocardiography, 1941, Lea and Febiger, Philadelphia, p. 524.
17. CLAGETT, A. H., JR.: Short P-R interval with prolonged QRS complex: allergic manifestations and unusual electrocardiographic abnormalities, Am. Heart Jr., 1943, xxvi, 55.
18. ARANA, R., and COSSIO, P.: Fibrilación auricular y taquicardia ventricular como eventualidad posible en el P-R corto con QRS ancho y mellado, Rev. argent. de cardiología, 1938, v, 43.

19. LEVINE, S. A., and BEESON, P. B.: The Wolff-Parkinson-White syndrome, with paroxysms of ventricular tachycardia, *Am. Heart Jr.*, 1941, xxii, 401.
20. ROBERTS, G. H., and ABRAMSON, D. I.: Ventricular complexes of the bundle branch block type associated with short P-R intervals, *Ann. Int. Med.*, 1936, ix, 983.
21. FOX, T. T., TRAVELL, J., and MOLOFSKY, L.: Action of digitalis on conduction in the syndrome of short PR interval and prolonged QRS complex, *Arch. Int. Med.*, 1943, lxxi, 206.
22. BISHOP, L. F.: Bundle branch block with short PR interval in individuals without organic heart disease: case report with review of the literature, *Am. Jr. Med. Sci.*, 1937, cxciv, 794.
23. WEDD, A. M.: Paroxysmal tachycardia, with reference to nomotropic tachycardia and the role of the extrinsic cardiac nerves, *Arch. Int. Med.*, 1921, xxvii, 571.
24. SIGLER, L. H.: Functional bundle branch block (partial) paradoxically relieved by vagal stimulation, *Am. Jr. Med. Sci.*, 1933, clxxxv, 211.
25. SCHERF, D., and SCHONBRUNNER, E.: Beiträge zum Problem der verkürzten Vorhofkammerleitung, *Ztschr. f. klin. Med.*, 1935, cxxviii, 750.
26. MOIA, B., and INCHAUSPE, L. H.: Sobre un caso de PR sorto con QRS ancho y melado presentando asinchronismo ventricular, *Rev. argent. de cardiol.*, 1938, v, 114.
27. PARDEE, H. E. B.: Clinical aspects of the electrocardiogram, 1941, Paul B. Hoeber, New York, p. 132.
28. DEBOER, S.: Die Physiologie und Pharmakologie des Flimmerns, *Ergebn. d. Physiol.*, 1923, xxi, 1.

# CHOLINE AS AN ADJUVANT TO THE DIETARY THERAPY OF CIRRHOSIS OF THE LIVER \*

By A. H. RUSSAKOFF,† M.D., and HAROLD BLUMBERG, Sc.D.,  
*Baltimore, Maryland*

THE past several years have seen a change in the treatment of portal cirrhosis of the liver, particularly in regard to the rôle of diet in therapy. This is especially true of alcoholic cirrhosis, the type which constitutes a majority of the cases of cirrhosis observed in the United States (Ratnoff and Patek <sup>1</sup>). The change has been brought about by experimental and clinical observations.

Connor <sup>2, 3</sup> emphasized the importance of prolonged fatty infiltration of the liver in the development of cirrhosis in diabetes and in chronic alcoholism. Experimental support for this theory was found in 1938 when Chaikoff, Connor, and Biskind <sup>4</sup> observed cirrhosis in depancreatized dogs long maintained with insulin, and Connor and Chaikoff <sup>5</sup> produced cirrhosis in dogs that had been fed a high fat diet and alcohol. The primary etiological importance of diet, rather than alcohol, was subsequently indicated by the production of cirrhosis in rats fed high fat, low protein diets (Blumberg, <sup>6</sup> Blumberg and Grady <sup>7, 8</sup>) and in dogs fed a high fat diet without alcohol (Chaikoff and Connor, <sup>9</sup> Chaikoff, Eichorn, Connor, and Entenman <sup>10</sup>).

In 1939 György and Goldblatt <sup>11</sup> reported two instances of fibrosis and two instances of localized cirrhosis in a large group of rats on diets deficient in parts of the vitamin B complex. Rich and Hamilton <sup>12, 13</sup> produced in rabbits a diffuse portal cirrhosis, resembling Laennec's cirrhosis in man, and associated this effect with the absence of yeast. The respective approaches of high fat diet and nutritional deficiency in the rat were brought closer together by reports of hepatic damage (necrosis, cirrhosis) on moderately high fat, low protein, choline deficient diets to which the addition of choline with yeast or with cystine had a beneficial effect (György and Goldblatt <sup>14, 15</sup>), and through the prevention by choline of a fatty cirrhosis produced by high fat, low protein, choline deficient diets (Blumberg and Grady, <sup>16</sup> Blumberg and McCollum <sup>17</sup>). Cirrhosis was also produced on low protein, choline deficient diets that were low in fat, and prevention was secured by the addition of choline (Lillie, Daft, and Sebrell, <sup>18</sup> Daft, Sebrell, and Lillie <sup>19</sup>). Betaine hydrochloride, which is closely related chemically to choline, was also used to prevent cirrhosis in rats (Webster <sup>20</sup>). Cirrhosis was produced in rabbits on diets in which choline deficiency was not believed to be a factor (Spellberg and Keeton, <sup>21</sup> Spellberg, Keeton, and Ginsberg <sup>22</sup>); however,

\* Received for publication May 23, 1944.

From the Medical Service, Sinai Hospital (A.H.R.), and the Department of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University (H.B.)

† Formerly Resident in Medicine, Sinai Hospital, Baltimore, Maryland; now Assistant Surgeon (R), U. S. Public Health Service.

under different conditions and with a purified diet, a retarding or preventive action in rabbits was found (Blumberg, Mackenzie, and Seligson<sup>23</sup>). A beneficial effect of choline was observed in dietary cirrhosis of dogs, although the preventive action was not complete (Fouts<sup>24</sup>).

The effectiveness of choline in removing fat from the liver was discovered by Best, Hershey, and Huntsman<sup>25, 26</sup> in 1932. Presumably the beneficial or preventive action of choline in experimental cirrhosis is due to this lipotropic activity, although some other mechanism, perhaps affecting cystine metabolism, may also be involved. It has been demonstrated that cystine may produce a non-fatty portal cirrhosis in rats when fed at the excessive, toxic levels of 5 or 10 per cent of the diet (Earle and Victor<sup>27</sup>).

Beneficial or protective action in rats was also secured with high levels of protein (casein),<sup>15, 19, 20, 23</sup> as well as with moderate amounts of the amino acid, methionine,<sup>17, 19, 15, 23</sup> the choline precursor in which casein is relatively rich. Large amounts of yeast, which contains choline, have also been found to be protective,<sup>14, 23</sup> although it must be noted that samples of yeast vary considerably in choline content and sometimes may have only very small amounts. Large amounts of casein have also proved protective in dogs.<sup>24</sup>

Dietary treatment cannot be expected to "cure" experimental cirrhosis in the sense of removing the fibrosis. However, the excellent experiments of Lowry, Daft, Sebrell, Ashburn, and Lillie<sup>28</sup> demonstrated that oral therapy with choline or with large amounts of casein can arrest the cirrhotic process in rats, as indicated by survival, improved general condition, regression of fatty changes and decrease in liver size, and improved appearance of liver cells. Arrest of the cirrhotic process has also been obtained with methionine therapy (Blumberg<sup>29</sup>).

Renewed clinical interest in the dietary management of cirrhosis was stimulated in 1937, when Patek<sup>30</sup> reported that patients with alcoholic cirrhosis appeared to benefit significantly from a generally nutritious, high vitamin diet. These preliminary findings were extended by Patek and Post<sup>31</sup> and Patek<sup>32</sup> in their subsequent study of a series of 54 cirrhotic patients who received a highly nutritious diet (including ample protein) supplemented by concentrates of the vitamin B complex. Fleming and Snell<sup>33</sup> (also Snell,<sup>34</sup> Butt and Snell<sup>35</sup>) likewise observed a favorable influence of diet in a group of 50 patients who received large amounts of vegetable proteins, carbohydrates, and vitamins. In connection with their studies on the treatment of alcoholic neuropathies, Goodhart and Jolliffe<sup>36</sup> and Wayburn and Guerard<sup>37</sup> mentioned incidental improvement in the general condition of some of the cirrhotic patients during the treatment with thiamine and vitamin B concentrates.

From pathological observations there is evidence that hepatic cirrhosis is associated frequently with extensive fatty infiltration of the liver (Connor,<sup>2, 3</sup> Keefer and Fries<sup>38</sup>). From chemical analysis of autopsy material, it is indicated that many cirrhotic livers have a greatly increased content of

neutral fat (Ralli, Paley, and Rubin,<sup>39</sup> Thannhauser and Reinstein<sup>40</sup>), the type of lipid upon which the lipotropic action of choline is very effective. In animal experiments it has been shown that choline has a beneficial effect in the prevention or treatment of certain types of dietary fatty cirrhosis. In view of these pathological, chemical, and nutritional data, it seemed desirable to investigate the possible value of choline as an adjuvant to the dietary treatment of clinical cirrhosis of the liver. While this study was progressing, Broun and Muether<sup>41</sup> published an abstract on the favorable effect of choline in four cases of cirrhosis. Our experience with the use of choline and dietary therapy has been sufficiently encouraging to warrant a report of the results in 10 patients studied during the past two years.

#### CASE REPORTS \*

*Case 1.* T. P., a 41 year old, white, married female with a long history of alcoholism and dietary insufficiency, was admitted to the Sinai Hospital on June 20, 1942, because of jaundice and persistent bleeding from tooth sockets following the extraction of several teeth. In the recent past she had noted numbness of the extremities, edema of the legs, gnawing epigastric pain, transient jaundice, dyspnea on exertion, and swelling of the abdomen. On admission the temperature, pulse, and respirations were slightly elevated. She was dyspneic, orthopneic, icteric, "nervous," and mildly confused. The tongue was beefy red, and despite attempts at local hemostasis, blood continued to ooze freely from the tooth sockets. The face was covered with telangiectatic lesions, and over the upper chest and arms there were numerous spider angiomas. Pitting edema extended from the legs up to the costal margins. The heart and lungs were essentially normal. The abdomen was markedly distended with fluid, and the abdominal wall was traversed by an extensive superficial collateral venous pattern. The spleen could not be felt, but the liver edge was tender and ballottable six fingers' breadth below the right costal margin. There were gross tremors of the upper extremities, with paresthesia and hyporeflexia of the lower extremities.

The hemogram on admission revealed a moderately severe anemia. The leukocyte count rose from 10,000 per cu.mm. to 25,000 per cu.mm. within the first few hospital days. Other initial laboratory data revealed a greatly prolonged prothrombin time, an icterus index of 50, a marked bromsulfalein retention, and poor hippuric acid excretion, but normal values for the blood urea, serum proteins, albumin-globulin ratio, and serum cholesterol and esters. The serological test for syphilis was negative.

The patient was transfused and given a vitamin K preparation intravenously in large amounts, with a gradual cessation of gingival bleeding as the prothrombin time became less prolonged. A preparation of vitamin B complex (containing thiamine, riboflavin, nicotinic acid, and pantothenic acid) and various fractions thereof were administered parenterally in massive dosage. The patient was able to take but small quantities of the prescribed high protein, high carbohydrate, low fat diet. One week after admission the patient had a generalized convulsion and lapsed into coma. During the ensuing days the course was ingravescent. She remained comatose for days, with rare momentary remissions of semistupor. The icterus index rose to 200, the blood urea rose to 200 mg. per cent, the serum proteins fell to 5.6 gm. per cent with a

\* With the exception of the omission of two cases with proved primary malignancy of the liver, these case reports represent an unselected series of patients with decompensated portal cirrhosis admitted to the Medical Wards of the Sinai Hospital of Baltimore from May, 1942, until December, 1943.

serum albumin of 2.8 gm. per cent, and the serum cholesterol fell to 89 mg. per cent, with esters of 80 mg. per cent. The edema became generalized, and signs of bronchopneumonia and myocardial insufficiency were manifest.

Twenty-five days after admission, while still uremic, cholemic, and in heart failure complicated by bronchopneumonia, the patient was started on tube-feedings of skimmed milk, egg white, glucose, and vitamins A and D. For lack of definite information as to the human adult oral dosage, we began to give 2.0 grams of choline chloride daily in divided doses. Within a few days it was noted that the patient became lucid and mildly conversational at rather frequent intervals. By the eighth day of this regimen, the edema of the upper extremities had disappeared completely and the patient had begun to ask for additional nourishment. The ascites diminished considerably, although the patient had never had an abdominal paracentesis. The serum proteins on this eighth day were 6.7 grams per cent with a serum albumin of 3.9 grams per cent. On the twelfth day, with further clinical improvement, the serum proteins had risen further to 7.6 grams per cent with a serum albumin of 4.5 grams per cent and the serum cholesterol was 175 mg. per cent with esters of 148 mg. per cent. The clotted blood at this time was found to be grossly lipemic. On the thirteenth day after the initiation of this regimen, the patient lapsed into severe pulmonary edema and died.

Postmortem examination revealed less than 200 c.c. of free fluid in the abdominal cavity. The liver was large and presented the gross and microscopic picture of advanced portal cirrhosis. The lungs were edematous and showed foci of bronchopneumonia. In addition, there was chronic cholecystitis with cholelithiasis.

Although this advanced case of cirrhosis terminated in death, the striking improvement subsequent to the administration of choline stimulated further testing of choline therapy.

*Case 2.* L. S., a 43 year old, white, divorced, female patient with a long history of alcoholism and dietary insufficiency, was admitted in May, 1942. Four months before admission, she had a hematemesis followed by melena and jaundice. Ascites appeared one week later and persisted thereafter. Liver function tests at that time were abnormally low, and esophageal varices were demonstrable. The serum proteins were 6.1 grams per cent with a serum albumin of 4.2 grams per cent. The serological test for syphilis was negative. She was treated for a month with a high carbohydrate diet, mercurial diuretics, and repeated abdominal paracenteses without improvement. During this regimen, spider angiomas and chloasmic lesions appeared.

She was readmitted in July, 1942, for a test with choline. Physical examination at that time revealed the common stigmata of decompensated portal cirrhosis, the liver and spleen extending three fingers' breadth below the costal margins. There was a normochromic anemia with a leukopenia. For two weeks the patient was treated with a high protein, high carbohydrate, low fat diet without clinical improvement. Liver function tests showed no laboratory evidence of improvement. Choline chloride was administered then in doses of 0.5 gram thrice daily, and on the fourth day the patient began to lose weight. During a period of 30 days the patient's weight dropped from 157 to 134 pounds, in association with a diminution in abdominal girth of five inches and the complete disappearance of ascites.

On follow-up examinations over a period of 18 months, the patient has remained free of ascites, the serum proteins have risen to 7.4 grams per cent with a serum albumin of 5.0 grams per cent, the skin lesions have waned, the spleen has receded to the left costal margin, the liver is smaller, the blood picture is normal, esophageal varices are no longer demonstrable, there has been a return of the normal menstrual cycle after almost a year of complete amenorrhea, and the patient has remarried happily. She has continued on the prescribed diet and choline, and has abstained from alcohol except socially.



*Case 3.* L. G., a 57 year old, married housewife, with a history of alcoholism, was admitted in July, 1941, because of dyspnea following the passage of a tarry stool. She was found to have a hepato-splenomegaly, ankle edema, and a marked secondary anemia. On bed rest and a high carbohydrate diet, the edema disappeared, she lost 20 pounds, and she was discharged improved. She was readmitted one year later with ankle edema, ascites, hepato-splenomegaly, and anemia. Liver function tests were below normal, and the serum proteins were 5.6 grams per cent with a serum albumin of 3.3 grams per cent. The serological test for syphilis was doubtful on a few occasions, but negative on many others. Serological tests for syphilis on the spinal and ascitic fluids were negative, and there were no stigmata of syphilis.

The patient was treated for two weeks with a high protein, high carbohydrate, low fat diet without benefit. During this period an abdominal paracentesis was necessary. Choline chloride was begun in doses of 0.5 gm. four times daily. During the succeeding three weeks the edema and ascites disappeared, and there was an associated loss of weight, a diminution of girth, and a feeling of well-being. She was discharged markedly improved on diet and choline.

On monthly follow-up examinations, the patient continued to improve. There was no recurrence of ascites; there was improvement in the liver function tests, associated with a rise in serum proteins to 7.1 grams per cent with a serum albumin of 4.9 grams per cent, and a remarkable increase in energy.

After six months of good health, the patient resorted to alcohol again, took an inadequate diet, and ceased to take choline regularly. She returned to the hospital but was uncoöperative and left against advice. She died at home several weeks later.

*Case 4.* E. P., a 27 year old, white, married housewife, with a long history of alcoholism and dietary inadequacy, gastrointestinal disturbances, recurrent icterus, neuritis, and non-traumatic epistaxes, was admitted in December, 1942, because of increasing jaundice and abdominal distention.

She was found to be anemic, was deeply jaundiced, showed evidence of thiamine, riboflavin, and nicotinic acid deficiency. She had an inactive mitral valvulitis. The abdomen was greatly distended with free fluid. The liver edge was palpable five fingers' breadth below the right costal margin, and splenic dullness was increased. There was edema of the lower extremities.

The hemogram revealed a macrocytic hyperchromic anemia, with a leukocytosis and a shift to the left. The serological test for syphilis was negative. The blood urea and non-protein nitrogen were normal, the icterus index was 100, the prothrombin time was prolonged, the bromsulfalein retention 40 per cent, the serum cholesterol 73 mg. per cent with esters of 29 mg. per cent, and the serum proteins were 8.2 grams per cent with a serum albumin of 5.1 grams per cent.

The patient could not tolerate the prescribed diet. Two abdominal paracenteses were performed, and generous supplements of a vitamin B complex preparation and of a vitamin K preparation were given parenterally. Choline chloride was administered in doses up to six grams daily. Nevertheless, she developed signs of bronchopneumonia, lapsed into pulmonary edema, and died on the fifth hospital day.

Autopsy revealed portal cirrhosis of the liver with splenomegaly, ascites, and esophageal varices. There was evidence of an inactive mitral valvulitis, pulmonary edema, and bronchopneumonia. The pathologist stated that microscopic sections of this liver showed fat throughout the entire hepatic parenchyma.

*Case 5.* J. C., a 53 year old, non-alcoholic, white male, was admitted in February, 1943, because of abdominal swelling. His past history was of significance in that he had been treated with duodenal drainage for a condition about which he remembered little, some 25 years before admission, and that for years he had been on a diet grossly deficient in protein. About eight months before admission he developed abdominal swelling associated with weakness, dyspnea, and ankle edema, but he had

no gastrointestinal complaints or jaundice. He had recently been in another local hospital where he had been tapped and treated with a "nutritious" diet without benefit. Physical examination revealed an anemic, malnourished man who showed no signs of vitamin deficiency. The protuberant abdomen was traversed by dilated superficial veins; there was a demonstrable fluid wave and shifting dullness. The liver edge was found to be high under the right costal arch after abdominal paracentesis, and the spleen extended two fingers'-breadth below the left costal margin. Routine liver function tests were abnormally low, the serum proteins were 6.0 grams per cent with a serum albumin of 3.0 grams per cent, and the serological test for syphilis was negative.

Because of the marked abdominal distention, it was necessary to perform several abdominal paracenteses to afford the patient sufficient comfort to tolerate the prescribed high protein, high carbohydrate, low fat diet. Since the patient seemed to be getting worse clinically after a few weeks on diet alone, the serum proteins having fallen to 5.8 grams per cent with a serum albumin of 2.7 grams per cent, it was decided that choline chloride should be administered in doses of 4.5 grams daily. After two weeks the total proteins had risen to 6.5 grams per cent with a serum albumin of 4.2 grams per cent, and no further abdominal paracenteses were necessary. After 40 days of this therapeutic regimen, the serum proteins were 6.7 grams per cent with a serum albumin of 5.0 grams per cent. Associated with this response there was a diminution in the amount of ascites and a decrease in weight of 11 pounds. He was discharged markedly improved on diet and choline, but still had a small amount of ascites.

On follow-up examinations for nine months, his general health and nutrition were even better than on discharge. The amount of ascites had diminished slightly. He was at work and able to support his family again. He continued faithfully on diet and three grams of choline daily; and in December, 1943, the serum proteins were 7.0 grams per cent with a serum albumin of 5.4 grams per cent.

*Case 6.* R. W., a 56 year old, white bartender, with a history of alcoholism and periodic abstinence from food during a period of 20 years, was admitted in October, 1942, because of edema of the legs and swelling of the abdomen of several months' duration. On physical examination he was found to be sub-icteric and to have a left hydrothorax and ascites. The liver edge extended four fingers'-breadth below the right costal margin, and the spleen was easily palpable after abdominal paracentesis. There was marked pitting edema of both lower extremities and clubbing of the fingers.

The hemogram revealed a moderate normochromic anemia with a normal leukocyte and differential count. The serological test for syphilis was negative. Liver function tests were below normal, with serum proteins of 6.6 grams per cent and a serum albumin of 4.8 grams per cent. Tremendous esophageal varices were demonstrated.

The patient was tried on the adopted dietary regimen alone, but required repeated abdominal paracenteses to afford him sufficient comfort to tolerate food. Choline chloride was administered in doses up to five grams daily without demonstrable clinical improvement. Although he lapsed in and out of cholemia, the serum proteins rose to 7.2 grams per cent with a serum albumin of 5.0 grams per cent. Five weeks after admission, the patient had a lethal hemorrhage from a ruptured esophageal varix.

Autopsy showed a large but non-fatty cirrhotic liver, containing many extraordinary dense fibrotic sheets associated with an extensive collateral circulation about the lower end of the esophagus. There were also ascites, hydrothorax, splenomegaly, chronic cholecystitis, and cholelithiasis. From the gross and microscopic appearance of this liver, there was little that could have been expected therapeutically of lipotropic substances.

*Case 7.* A. W., a 58 year old, white male with a history of alcoholism, was

admitted in December, 1941, with ascites and ankle edema. A few years previously he had been found to have an enlarged liver and a positive serological test for syphilis, but subsequent examinations of blood and a spinal fluid examination were all negative for syphilis.

On physical examination, in addition to marked ascites, an extensive superficial abdominal collateral circulation, and edema of the legs, the patient was found to have an inactive mitral valvulitis with chronic auricular fibrillation, but without evidence of a constrictive pericarditis. The blood picture, the serum proteins, and serum albumin were normal. Studies of the ascitic fluid were negative for specific disease.

He was treated with a high carbohydrate, salt-free diet, vitamins, digitalis, mercurial diuretics, and abdominal paracenteses with only slight improvement. After abdominal taps, the liver edge was felt high under the right costal margin. The spleen was never felt. He was discharged on the forty-fifth hospital day.

He was readmitted nine months later, having adhered to the prescribed regimen without improvement. Abdominal paracenteses, averaging approximately 10 liters each, were necessary every four weeks. The physical findings were unchanged. The hemogram was normal, the bromsulfalein retention was 20 per cent in 30 minutes, and the serum proteins were 5.2 grams per cent with a serum albumin of 2.2 grams per cent.

In addition to digitalis, the patient was given a high protein, high carbohydrate, low fat diet supplemented with six grams of choline chloride daily. On this regimen during the 90 day hospital stay and during the subsequent 90 day follow-up period, the serum proteins rose to 6.5 grams per cent with a serum albumin of 4.6 grams per cent, and the bromsulfalein retention dropped to 5 per cent in 30 minutes. Nevertheless, he required six abdominal paracenteses.

Because the osmotic factor had been well cared for and the cardiac status was of minor import, we felt that the shrunken liver might exert a mechanical effect and thus be the major cause of the recurrences of ascites; so the patient was readmitted in May, 1943, for a sapheno-peritoneal anastomosis. A unilateral anastomosis was performed under local anesthesia by Dr. Louis J. Kolodner. The procedure was well tolerated, and during the past six months the patient has continued on the prescribed diet and 4.5 grams of choline daily. The serum proteins have risen further to 7.4 grams per cent with a serum albumin of 5.2 grams per cent and the patient has required only two abdominal paracenteses.

*Case 8.* V. W., a 62 year old, white, male alcoholic, was admitted in June, 1943. He had been well until one month before admission, when he noted jaundice, a change in the character of his stool, weight loss, ankle edema, and swelling of the abdomen. On physical examination he was obviously icteric, the abdomen was distended with fluid, and after abdominal paracentesis the liver edge was felt three fingers' breadth below the right costal margin. The spleen was not palpable. Edema was marked over the legs, and extended over the abdominal wall and sacrum.

There was a macrocytic hyperchromic anemia with a normal leukocyte and differential count. The serological test for syphilis was negative. Routine liver function tests were far below normal, the serum proteins were 5.8 grams per cent with a serum albumin of 3.9 grams per cent, the icterus index was 50, and esophageal varices were demonstrable in the esophogram.

On dietetic treatment alone the patient fared poorly, requiring abdominal paracenteses. Choline chloride was begun in doses of four to six grams daily, but the effect was not striking at first, for the patient required another abdominal tap. From this time until his discharge 45 days later, the patient improved steadily. The edema, ascites, and icterus disappeared, but the serum proteins and serum albumin were not altered appreciably. Nevertheless, the hemogram became normal without

transfusions, the esophageal varices were no longer demonstrable, and the bromsulfalein retention was 0 per cent in 30 minutes.

When seen on follow-up examinations, the patient had continued to improve, the serum proteins had risen to 7.6 grams per cent with a serum albumin of 5.2 grams per cent, and the patient was about to go back to work.

*Case 9.* O. B., a 31 year old, white, divorced female with a long history of alcoholism and dietary inadequacy, was admitted in September, 1943, with the diagnosis of pneumonia and decompensated cirrhosis of the liver. For more than a year before admission she had gastrointestinal complaints, transient jaundice, swelling of the abdomen, bleeding hemorrhoids, non-traumatic epistaxes, aberrations of the menstrual cycle, and symptoms of polyneuritis. Her weight prior to admission was approximately 155 pounds.

On admission the temperature was 104° F. (r), the pulse 136, the respirations 38, and the blood pressure 150 mm. Hg systolic and 95 mm. diastolic. The patient was dyspneic, cyanotic, edematous, and deeply icteric. She was slightly confused, and had a coarse tremor, the mousey odor of cholemia, and signs of consolidation of the lower lobe of the left lung associated with a diffuse bronchitis. The distended abdomen was traversed by an extensive collateral venous anastomosis, and showed shifting dullness and a fluid wave. The liver edge was nodular, tender, and extended nine fingers'-breadth below the right costal margin. The spleen was not palpable, but there were tenderness and increased splenic dullness in the left flank.

The hemogram revealed a mild normochromic anemia with a normal leukocyte and differential count. The serological test for syphilis was negative. The icterus index was 100, and there was a 55 per cent retention of bromsulfalein in 30 minutes. There was a moderate hypercholesterolemia with maintenance of a normal ester ratio. The serum proteins were 6.3 grams per cent with a serum albumin of 4.5 grams per cent. The urea, non-protein nitrogen and prothrombin times were normal, and the serum phosphatase was 10.5 Bodansky units.

A type IX pneumococcus was found in the sputum, and the patient was given oxygen and sulfadiazine in appropriate dosage for eight days without a notable response. Consequently, the sulfadiazine was stopped. From the outset, a high protein, high carbohydrate, low fat diet with vitamin supplements was forced. Choline chloride was begun on the third day in doses of 1.5 grams thrice daily. By the twentieth day the patient was afebrile, the pneumonia had resolved, the edema had disappeared, and the ascites had diminished. The serum proteins had risen to 7.0 grams per cent with a serum albumin of 5.1 grams per cent, the icterus index had dropped to 50, and the liver edge had receded to five fingers'-breadth below the costal margin.

Thereafter the patient's course was marked by continued improvement. During the next four weeks she became free of ascites, the icterus index dropped to 14, the bromsulfalein retention was 2 per cent in 30 minutes, and the serum phosphatase was 5.9 Bodansky units. No abdominal paracenteses were necessary, but the patient did receive three transfusions specifically for anemia during her early hospital stay. She was discharged after seven weeks, weighing 136½ pounds. She stated that she had not felt as well in years.

She has been ascites-free for three months and continues to enjoy excellent health. The serum proteins are now 8.5 grams per cent with a serum albumin of 6.2 grams per cent. The liver edge is now two to three fingers'-breadth below the costal margin, and there has been a return of her normal menstrual cycle. She has gained about 10 pounds, and her only complaint is of progressive alopecia, which is considered to be secondary to her severe illness.\*

*Case 10.* L. S., a 35 year old, white, male alcoholic, was admitted in November,

\* More recently there has been a return of scalp hair without medication.

1943, because of fatigue and recent swelling of the abdomen. There was a history of polyneuritis and gastrointestinal symptoms. On physical examination the patient was found to have a right hydrothorax, ascites, and a liver extending seven fingers'-breadth below the right costal margin, but no palpable spleen. The weight on admission was 157 pounds.

The hemogram showed a mild anemia. Liver function tests were normal, with serum proteins of 7.6 grams per cent and a serum albumin of 5.2 grams per cent. The serological test for syphilis was negative.

Since the patient was unable to tolerate the prescribed diet, an abdominal paracentesis was performed. Following this procedure, he took his diet well. Because the patient ran a remittent febrile course and was sensitive to high dilutions of tuberculo-protein, studies were carried out on both the pleural and ascitic fluid, which showed no evidence of tuberculosis. Roentgenographic studies of the chest revealed no evidence of tuberculosis or of Pick's disease.

On dietetic regimen alone for approximately three weeks, there was a diminution in the amount of ascites, and the patient's weight declined to and remained stationary at 145½ pounds. Choline chloride was begun in doses of 6.0 grams daily; there followed a further reduction in weight to 139½ pounds associated with less ascites and with a distinct improvement in general nutrition. Ten days after the initiation of choline therapy, the serum proteins were 8.0 grams per cent with a serum albumin of 5.6 grams per cent.

The patient was discharged on diet and choline. He was considerably improved and able to return to work, but still had demonstrable ascites.

In evaluating this group as a whole, and it is recognized that it does not have statistical significance, it is seen that four of this group of 10 patients are dead. Of these four, one died on the fifth hospital day of pulmonary edema complicated by bronchopneumonia (case 4). The extensive fatty infiltration of the liver suggested that much might have been expected therapeutically of lipotropic substances had the case not been complicated. A second patient (case 6), whose enlarged liver at autopsy was markedly scarred with dense sheets of fibrous tissue but contained very little fat, died of an exsanguinating esophageal hemorrhage. We believe that treatment can avail little in such instances in which the fibrotic process has advanced beyond the hope of improvement. Incidentally, this case illustrates that a large cirrhotic liver need not be a fatty liver.

Both of the remaining two deceased patients showed definite temporary improvement. Although the first (case 1) died in pulmonary edema complicated by bronchopneumonia, on the prescribed regimen she rallied briefly from a grave state, with an increase of serum proteins and serum albumin from extremely low figures to normal levels and a disappearance of edema and ascites. The second patient (case 3) died seven months after discharge. During this time she had been free of ascites and enjoyed good health until she resorted again to alcohol and neglected her diet and choline.

Of the six living patients, three have continued to be entirely free of ascites—one for 18 months (case 2), another for six months (case 8), and a third for three months (case 9). All three are rehabilitated to a relatively normal physical state and are adjusting socially. Of the remaining three patients with ascites, all have improved to some extent. One patient (case

7), who has a small shrunken liver and who has had ascites for at least two years, was hypoproteinemic and required abdominal paracenteses every four weeks prior to admission. On the prescribed regimen and a unilateral sapheno-peritoneal anastomosis, he goes 16 weeks without abdominal tapping. A second patient (case 5) has improved remarkably and has been working vigorously for nine months with a persistent small amount of ascites. The third (case 10), who was discharged from the hospital one month ago (December), is greatly improved and able to return to work.

In six instances diet alone was tried for several weeks without benefit. In three of these cases obvious responses were noted within a week after the addition of choline, and probable responses were subsequently noted in two of the other patients.

### DISCUSSION

There is a logical basis for the use of choline in the treatment of cirrhosis of the liver. Prior to the revolutionary work of Patek<sup>30</sup> and Patek and Post,<sup>31</sup> the mainstay of a rather hopeless therapeutic regimen was a diet high in carbohydrate and low in protein and fat. In their studies on a large group of cirrhotics, these workers have established firmly the value of a diet high in protein and in vitamins. Fleming, Snell, and Butt<sup>32, 34, 35</sup> have confirmed and adopted their general method. Experimental justification for this thesis is suggested by the work of Ravdin and coworkers (Ravdin, Thorogood, Riegel, Peters, and Rhoads<sup>42</sup>) on the chemical analysis of liver biopsies from surgical patients. Their studies demonstrated the protective effect that high protein diets afford the damaged liver, and also the associated reduction of liver fat. There can now be little doubt that diets rich in protein of high biological value are indicated in the presence of liver damage. The parenteral administration of amino acids in several cases of cirrhosis has been reported by Fagin and Zinn,<sup>43</sup> and evidence to suggest a lipotropic effect from such administration has been published by Fagin, Sahyun, and Pagel.<sup>44</sup> According to Hoagland,<sup>45</sup> soybean lecithin (which contains choline among other things) and parenteral crude liver extract are to be recommended.

There is rather general agreement that the deposition of fat precedes irreversible fibrotic changes in the pathogenesis of some types of portal cirrhosis, notably the alcoholic. It has been established by experiment that choline exerts a lipotropic effect, especially on neutral fat, and thus is capable of mobilizing fat from the fatty liver. On the basis of the aforementioned facts, there is a sound rationale for the use of choline in the treatment of cirrhosis of the liver in man. Indeed, since serious and fatal consequences may result from an enlarged fatty liver even in the absence of fibrosis (Connor,<sup>2</sup> Keefer and Fries,<sup>38</sup> LeCount and Singer,<sup>46</sup> Graham<sup>47</sup>), the use of choline in such cases may prove to be of decided value. It may be noted, incidentally, that Danis and Anderson<sup>48</sup> have observed beneficial effects from the use of choline chloride in three cases of icterus gravis neonatorum, a disorder with which a fatty liver is associated.

Despite the fact that the lipotropic effect of choline has been recognized for more than 10 years, we fail to find a single detailed clinical report on its use in the treatment of cirrhosis of the liver. In recording the efficacy of choline as an adjuvant to the already recommended high caloric, high protein, high carbohydrate, low fat, high vitamin diet on the basis of treating only seven cases with beneficial results, we do so to call attention to what may well be a helpful therapeutic agent; and our experience in the close observation of several patients, who failed to respond to the diet until choline was administered, lends strong support to this view. The possible rôle of another lipotropic substance, inositol (Gavin and McHenry,<sup>49</sup> Gavin, McHenry, and Patterson<sup>50</sup>), is yet to be investigated.

To our knowledge, the first clinical note on the use of choline in human cirrhosis was the abstract by Broun and Muether,<sup>41</sup> who were impressed favorably with their results in four cases. Yater, however, in a discussion<sup>51</sup> expressed a very unfavorable opinion: "During the last year I have used it (choline) perhaps in fifteen cases. Some of these patients went along and died promptly, not because of the choline but in spite of it. Other patients have remained about the same and some have improved. . . . it seems hardly likely to me from these cases and from reading the reports of a few others in which choline has been used that we can expect very much from this form of treatment." On the other hand, Gordon<sup>\* 52</sup> has stated (personal communication to the authors) that he has observed striking improvement in five cases of alcoholic cirrhosis treated with a combination of choline and cystine.

It is well known that the cirrhotic process may advance to an irreversible stage in which nothing is of much value. That this stage cannot be detected clinically even with the help of liver function tests is common knowledge to those who have had even a limited experience with this disease. Therefore, to condemn choline because improvement has not been observed in some few cases of decompensated portal cirrhosis in which it has been tested is comparable to doubting the efficacy of certain sulfonamides in the treatment of pneumococcal pneumonia because of the poor results noted in cases complicated by an overwhelming bacteremia; for the presence of persistent ascites in cirrhosis may be considered relatively as ominous as a severe sepsis complicating pneumonia. There is need for a study of a large, well-controlled group of cirrhotics and for an intelligent discrimination in appraising individual cases. In general, it seems that those patients having enlarged livers, and probably a fatty type of cirrhosis, will be most likely to respond favorably to choline therapy.

In the treatment of our cases, we prescribed a diet normal or high in calories, high in protein of good biological value (and rich in methionine), high in carbohydrate, and as low in fat as could be prepared easily by the

\* Dr. Edgar S. Gordon, University of Wisconsin School of Medicine, Madison, Wisconsin. (Now in Medical Corps, U. S. Army.)

dietitians and tolerated by the patients (C 250-300, P 125-200, F not more than 60). Lean meats, as well as skimmed milk and cottage cheese, were used freely as sources of protein. In several instances after a preliminary period on diet alone, choline was started. At first, due to timidity, small doses were prescribed; later, as much as six grams of choline chloride was administered daily in divided doses. We chose peppermint water as a solvent, for flavoring and for the specific purpose of denying our patients even the small amounts of alcohol present in an elixir. No unfavorable reactions were encountered when choline was administered in this manner after meals. However, when three patients after an overnight fast were given 0.5 gram of choline chloride without food, one experienced nausea without vomiting. This was associated with a very slight drop in blood pressure and a slight slowing of the heart rate. One patient had no untoward effects during the administration of as much as six grams of choline chloride daily for six months.

Our patients received vitamin supplements, although not in the heavy dosage sometimes recommended by others. We gave 1 c.c. of a standard preparation of vitamin B complex parenterally to several patients who had no clinical evidences of deficiency; large doses of the various fractions were administered when indicated. Only one of our patients received powdered yeast, which is an inconstant and at times a very poor source of choline, because the primary purpose of the study was to evaluate the efficacy of choline. Some observers have found crude liver extract beneficial in some refractory cases of cirrhosis. We used none. Vitamin K was given parenterally to all jaundiced patients without regard to the prothrombin time. Non-icteric patients with increased prothrombin time received vitamin K by mouth. One patient received as much as 10 mg. of a vitamin K preparation intravenously several times daily to control bleeding (case 1). We prescribed 15,000 to 20,000 U.S.P. units of vitamin A and 1,500 to 2,000 U.S.P. units of vitamin D daily. No bile salt therapy was used in this group of cases.

Abdominal paracenteses were performed in eight of the ten cases as frequently as was necessary to afford the patient sufficient comfort to take all of his therapeutic diet. This we consider to have been of fundamental importance. Transfusions of whole blood were given in a few instances specifically for anemia.

Improvement was gauged by the clinical response of the patients correlated with alteration of the laboratory data. An increase of the serum proteins, and more specifically of the serum albumin, above the critical level was usually associated with a spontaneous diuresis, a loss of weight, a diminution of girth, the disappearance of edema and ascites, the subsidence of icterus, a feeling of well being, an improvement in appetite, the resumption of the normal menstrual cycle in female patients, and the freedom from the necessity of further abdominal paracenteses except in one case (case 7).



In the patients with hepatomegaly, there usually appeared to be a decrease in the size of the liver. These clinical responses were associated usually with improvement in liver function tests, a diminution in the icterus index, a decrease in prothrombin time, and improvement in the blood picture in those patients who presented abnormalities of one or more of these determinations. The speed of response in those who improved was variable. Three patients responded within a week after the administration of choline was started. Others responded more slowly.

### SUMMARY

1. The course of ten patients with decompensated portal cirrhosis of the liver, who have been treated with a high caloric, high protein, high carbohydrate, low fat diet, the usual vitamins, and choline, has been presented.

2. Of the nine patients treated adequately with this regimen, seven improved. Three of these patients manifested little or no change when treated first for several weeks with the high protein diet alone, but showed distinct improvement within a week after the beginning of choline therapy.

3. A review of the literature on the relation of choline to cirrhosis has been presented.

4. There seems to be justification for the use of choline as an adjuvant to the dietary therapy of cirrhosis of the liver, particularly of the fatty, alcoholic type.

The authors are indebted to Drs. Charles Austrian, Samuel Wolman, and Tobias Weinberg, and to the many internes and technicians who gave their interest and co-operation in this study. The interest and advice of Professor E. V. McCollum is gratefully acknowledged.

The supplies of choline chloride to inaugurate this study were provided through the courtesy of Merck and Co., Inc., Rahway, N. J.

Acknowledgment is made to the Edwin B. Hutzler Research Fund of Sinai Hospital for supplying choline chloride for the patients in this study over a period of two years.

### BIBLIOGRAPHY

1. RATNOFF, O. D., and PATEK, A. J., JR.: The natural history of Laennec's cirrhosis of the liver, *Medicine*, 1942, xxi, 207-268.
2. CONNOR, C. L.: Fatty infiltration of the liver and the development of cirrhosis in diabetes and chronic alcoholism, *Am. Jr. Path.*, 1938, xiv, 347-364.
3. CONNOR, C. L.: The etiology and pathogenesis of alcoholic cirrhosis of the liver, *Jr. Am. Med. Assoc.*, 1939, cxii, 387-390.
4. CHAIKOFF, I. L., CONNOR, C. L., and BISKIND, G. R.: Fatty infiltration and cirrhosis of the liver in depancreatized dogs maintained with insulin, *Am. Jr. Path.*, 1938, xiv, 101-110.
5. CONNOR, C. L., and CHAIKOFF, I. L.: Production of cirrhosis in fatty livers with alcohol, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 356-359.
6. BLUMBERG, H.: Attempts to produce tumors in rats by feeding crude wheat germ oil made by prolonged ether extraction, *Pub. Health Rep.*, 1940, lv, 531-537.
7. BLUMBERG, H., and GRADY, H. G.: The production of diffuse nodular cirrhosis of the liver in rats on high fat-low protein diets, *Jr. Biol. Chem.*, 1941, cxl, 15.
8. BLUMBERG, H., and GRADY, H. G.: Production of cirrhosis of the liver in rats by feeding low protein, high fat diets, *Arch. Path.*, 1942, xxxiv, 1035-1041.

9. CHAIKOFF, I. L., and CONNOR, C. L.: Production of cirrhosis of the liver of the normal dog by high fat diets, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 638-641.
10. CHAIKOFF, I. L., EICHORN, K. B., CONNOR, C. L., and ENTENMAN, C.: The production of cirrhosis in the liver of the normal dog by prolonged feeding of a high-fat diet, *Am. Jr. Path.*, 1943, xix, 9-21.
11. GYÖRGY, P., and GOLDBLATT, H.: Hepatic injury on a nutritional basis in rats, *Jr. Exper. Med.*, 1939, lxx, 185-192.
12. RICH, A. R., and HAMILTON, J. D.: The experimental production of cirrhosis of the liver by means of a deficient diet, *Bull. Johns Hopkins Hosp.*, 1940, lxvi, 185-198.
13. RICH, A. R., and HAMILTON, J. D.: Further studies on cirrhosis of the liver produced by a dietary deficiency, *Trans. Assoc. Am. Phys.*, 1940, lv, 133-139.
14. GYÖRGY, P., and GOLDBLATT, H.: Experimental production of dietary liver injury (necrosis, cirrhosis) in rats, *Proc. Soc. Exper. Biol. and Med.*, 1941, xlv, 492-494.
15. GYÖRGY, P., and GOLDBLATT, H.: Observations on the conditions of dietary hepatic injury (necrosis, cirrhosis) in rats, *Jr. Exper. Med.*, 1942, lxxv, 355-368.
16. BLUMBERG, H., and GRADY, H. G.: Read before American Society for Experimental Pathology, Chicago, April 19, 1941.
17. BLUMBERG, H., and McCOLLUM, E. V.: The prevention by choline of liver cirrhosis in rats on high fat, low protein diets, *Science*, 1941, xciii, 598-599.
18. LILLIE, R. D., DAFT, F. S., and SEBRELL, W. H., JR.: Cirrhosis of the liver in rats on a deficient diet and the effect of alcohol, *Pub. Health Rep.*, 1941, lvi, 1255-1258.
19. DAFT, F. S., SEBRELL, W. H., and LILLIE, R. D.: Production and apparent prevention of a dietary liver cirrhosis in rats, *Proc. Soc. Exper. Biol. and Med.*, 1941, xlviii, 228-229.
20. WEBSTER, G. T.: Cirrhosis of the liver among rats receiving diets poor in protein and rich in fat, *Jr. Clin. Invest.*, 1942, xxi, 385-392.
21. SPELLBERG, M. A., and KEETON, R. W.: The production of fatty and fibrotic livers in guinea pigs and rabbits by seemingly adequate diets, *Am. Jr. Med. Sci.*, 1940, cc, 688-697.
22. SPELLBERG, M. A., KEETON, R. W., and GINSBERG, R.: Dietary production of hepatic cirrhosis in rabbits, *Arch. Path.*, 1942, xxxiii, 204-217.
23. BLUMBERG, H., MACKENZIE, C. G., and SELIGSON, D.: The prevention by choline, methionine, or casein of dietary cirrhosis of the liver in rats and rabbits, *Federation Proc.*, 1942, i, 187.
24. FOUTS, P. J.: Vitamin B complex studies in dogs: production of cirrhosis of liver, *Jr. Nutr.*, 1943, xxv, 217-228.
25. BEST, C. H., HERSHEY, J. M., and HUNTSMAN, M. E.: The control of the deposition of liver fat, *Am. Jr. Physiol.*, 1932, ci, 7.
26. BEST, C. H., and HUNTSMAN, M. E.: The effects of the components of lecithine upon deposition of fat in the liver, *Jr. Physiol.*, 1932, lxxv, 405-412.
27. EARLE, D. P., JR., and VICTOR, J.: Cirrhosis of the liver caused by excess dietary cystine, *Jr. Exper. Med.*, 1941, lxxiii, 161-172.
28. LOWRY, J. V., DAFT, F. S., SEBRELL, W. H., ASHBURN, L. L., and LILLIE, R. D.: Treatment of dietary liver cirrhosis in rats with choline and casein, *Pub. Health Rep.*, 1941, lvi, 2216-2219.
29. BLUMBERG, H.: Unpublished data.
30. PATEK, A. J., JR.: Treatment of alcoholic cirrhosis of the liver with high vitamin therapy, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvii, 329-330.
31. PATEK, A. J., JR., and POST, J.: Treatment of cirrhosis of the liver by a nutritious diet and supplements rich in vitamin B complex, *Jr. Clin. Invest.*, 1941, xx, 481-505.
32. PATEK, A. J., JR.: Dietary treatment of Laennec's cirrhosis with special reference to early stages of the disease, *Bull. New York Acad. Med. (second Series)*, 1943, xix, 498-506.

33. FLEMING, R. G., and SNELL, A. M.: Portal cirrhosis with ascites: An analysis of 200 cases with special reference to prognosis and treatment, *Am. Jr. Digest. Dis.*, 1942, ix, 115-120.
34. SNELL, A. M.: Recent advances in the treatment of hepatic disease, *Minnesota Med.*, 1940, xxiii, 551-556.
35. BUTT, H. R., and SNELL, A. M.: Recent trends in treatment of cirrhosis of the liver, *Proc. Staff Meet. Mayo Clin.*, 1942, xxvii, 250-254.
36. GOODHART, R., and JOLLIFFE, N.: Effects of vitamin B ( $B_1$ ) therapy on the polyneuritis of alcohol addicts, *Jr. Am. Med. Assoc.*, 1938, cx, 414-418.
37. WAYBURN, E., and GUERARD, C. R.: Relation between multiple peripheral neuropathy and cirrhosis of the liver, *Arch. Int. Med.*, 1940, lxvi, 161-172.
38. KEEFER, C. S., and FRIES, E. D.: The fatty liver—its diagnosis and clinical course, *Trans. Assoc. Am. Phys.*, 1942, lvii, 283-288.
39. RALLI, E. P., PALEY, K., and RUBIN, S. H.: The liver lipids and their distribution in disease. An analysis of 60 human livers, *Jr. Clin. Invest.*, 1941, xx, 413-417.
40. THANNHAUSER, S. J., and REINSTEIN, H.: Fatty changes in the liver from different causes: comparative studies of the lipid partition, *Arch. Path.*, 1942, xxxiii, 646-654.
41. BROUN, G. O., and MUETHER, R. O.: Treatment of hepatic cirrhosis with choline chloride and diet low in fat and cholesterol. *Proc. Central Soc. Clin. Res.*, in *Jr. Am. Med. Assoc.*, 1942, cxviii, 1403.
42. RAVDIN, I. S., THOROGOOD, E., RIEGEL, C., PETERS, R., and RHOADS, J. E.: The prevention of liver damage and the facilitation of repair in the liver by diet, *Jr. Am. Med. Assoc.*, 1943, cxxi, 322-325.
43. FAGIN, I. D., and ZINN, F. T.: Cirrhosis of the liver: results of treatment with parenterally administered amino acids, *Jr. Lab. and Clin. Med.*, 1942, xxvii, 1400-1409.
44. FAGIN, I. D., SAHYUN, M., and PAGEL, R. W.: Cirrhosis of the liver: the lipotropic action of parenterally administered amino acids, *Jr. Lab. and Clin. Med.*, 1943, xxviii, 987-993.
45. HOAGLAND, C. L.: In *Conferences on Therapy: The modern treatment of cirrhosis of the liver and hepatic insufficiency*, New York State Jr. Med., 1943, xliii, 1041-1048.
46. LECOUNT, E. R., and SINGER, H. A.: Fat replacement of the glycogen in the liver as a cause of death, *Arch. Path. Lab. Med.*, 1926, i, 84-89.
47. GRAHAM, R. L.: Sudden death in young adults in association with fatty liver, *Bull. Johns Hopkins Hosp.*, 1944, lxxiv, 16-25.
48. DANIS, P. G., and ANDERSON, W. A. D.: Choline chloride in the treatment of icterus gravis neonatorum, *South. Med. Jr.*, 1942, xxxv, 1070-1076.
49. GAVIN, G., and MCHENRY, E. W.: Inositol: a lipotropic factor, *Jr. Biol. Chem.*, 1941, cxxxix, 485.
50. GAVIN, G., PATTERSON, J. M., and MCHENRY, E. W.: Comparison of the lipotropic effects of choline, inositol, and lipocaic in rats, *Jr. Biol. Chem.*, 1943, cxlviii, 275-279.
51. YATER, W. M.: In discussion of paper by C. H. GREENE, *Jr. Am. Med. Assoc.*, 1943, cxxi, 720.
52. GORDON, E. S.: Personal communication.

# PRIMARY AND SECONDARY MYELOFIBROSIS (A CLINICAL AND PATHOLOGICAL STUDY OF THIRTEEN CASES OF FIBROSIS OF THE BONE MARROW) \*

By LOWELL A. ERF, M.D., F.A.C.P., and PETER A. HERBUT, M.D.,  
*Philadelphia, Pennsylvania*

MYELOFIBROSIS means fibrosis of the bone marrow. The process may be either focal or generalized, primary or secondary, mild or severe, and may or may not be associated with various degrees of myelosclerosis (defined as an excessive proliferation of endosteal bone, known also as osteosclerosis) in any or all bones of the body. Among others, fibrosis of the bone marrow has been observed in the following conditions:

## A. Focal:

### I. Primary (idiopathic),

1. Such a condition has not been described unless Albright's disease<sup>1</sup> can be considered as such, or
2. Monomelic medullary osteosclerosis<sup>2</sup> (case 1, table 1).

### II. Secondary to (in certain cases),

1. Various bone diseases,
  - a. Focal osteitis fibrosa.<sup>3</sup>
  - b. Various congenital bone diseases.<sup>4, 5</sup>
  - c. Paget's disease.<sup>4, 5</sup>
  - d. Osteomyelitis (clinical and experimental).
  - e. About sites of bone tumors; temporarily about sites of fractures.
2. Albright's disease.<sup>6, 7</sup>
3. The majority of the conditions listed under B. "Generalized" and II, "Secondary" may have only associated focal myelofibrosis.
4. Experimental,
  - a. Occlusion of nutrient vessels to marrow (not by ligation,<sup>8</sup> but by multiple infarction<sup>9</sup>).
  - b. Transplantation of marrow to anterior chamber of eye (see Discussion).

\* Presented at the Meeting of the Pathological Society at College of Physicians, Philadelphia, February 10, 1944. Received for publication March 11, 1944.

From the Charlotte Drake Cardeza Foundation, the Department of Medicine and the Clinical Laboratories, Jefferson Medical College Hospital, Philadelphia.

## B. Generalized:

## I. Primary (idiopathic),

1. Myelofibrosis<sup>10, 11</sup> (cases 2-6, table 1).

Myelofibrosis has been a prominent feature in many cases described as,

- a. Leukanemia (Leube and Arneth<sup>12</sup>).
- b. Chronic splenomegaly with anemia and myeloid reaction in the blood (Weil and Clerc).
- c. Splenomegaly of myeloid type with myelocythemia (Rathery).
- d. Myeloid splenic anemia (Vaquez and Aubertin).
- e. Atypical myeloid leukemia or aleukemic myelosis (Hirschfeld).
- f. Chronic non-leukemic myelosis (Hickling<sup>12</sup>).
- g. Myelosclerosis (Mozer).
- h. Osteosclerotic anemia (Rusk and Miles; Chapman).
- i. Myelophthisic splenomegaly (Ballin and Morse).
- j. Aleukemic myelosis with osteosclerosis (Stephens and Bredeck).
- k. Leukoerythroblastic anemia with diffuse osteosclerosis (Mendeloff and Rosenthal).
- l. Splenomegaly with myeloid transformation (Tudhope).
- m. Marrow sclerosis associated with massive myeloid splenomegaly (Taylor and Smith).
- n. Megakaryocytic myelosis with osteosclerosis (Hewer).
- o. Generalized osteosclerosis (Parkes-Weber<sup>13</sup>).
- p. Hemopoietic splenomegaly with marrow sclerosis (Wade).
- q. Myeloid megakaryocytic hepato-splenomegaly (Downey and Nordland).
- r. Agnogenic myeloid metaplasia (Jackson, Parker and Lemon<sup>70</sup>).

## II. Secondary to (in certain cases),

## 1. Various bone diseases and metastases to bones,

a. Generalized osteoporosis.<sup>14</sup>

Osteogenesis imperfecta cystica.

Infantile scurvy.

Osteomalacia.

Renal rickets.

b. Generalized increased density of bone,<sup>14</sup>

Diffuse fibrosis of bone (often progresses from a porotic to a petrosic condition).

Melorheostosis.

Osteopetrosis.<sup>11</sup>

Leontiasis ossea.

Osteitis deformans (Paget's disease).<sup>14</sup>

Osteitis fibrosa cystica (Von Recklinghausen's disease).

- c. Metastases to bone<sup>14, 15, 16, 17, 18</sup> (cases 9–12, table 1),
  - a'. Osteolytic (as in cases with cancer of breast or kidney).
  - b'. Osteoplastic (as in cases with cancer of prostate and stomach).<sup>58</sup>
  - c'. Pagetoid (as in cases with cancer of prostate, stomach, colon or breast).
  - d'. Cyst-like (as in cases with hypernephroma or in cases with cancer of the thyroid gland).
2. Myelosclerosis.<sup>19, 20, 21</sup>
3. Myeloma<sup>22</sup> and tumors of bone marrow (case 13, table 1).
4. Polycythemia.<sup>11, 18, 19, 23</sup>
5. Leukemia<sup>10, 11, 12, 18, 24, 69</sup> (case 7, table 1).
6. Hodgkin's disease.<sup>25, 26</sup> (case 8, table 1).
7. Gaucher's disease.<sup>16</sup>
8. Amyloid disease.<sup>16</sup>
9. Xanthomatosis.<sup>6</sup>
10. Erythroblastosis.<sup>27</sup>
11. Septicemia.<sup>11</sup>
12. Renal disease.<sup>7</sup>
13. Poisonings,
  - a. Benzene.<sup>28</sup>
  - b. Fluorine.<sup>29</sup>
  - c. Irradiations; chronic,<sup>30</sup> not acute.<sup>31</sup>
14. Experimental,
  - a. Strontium.<sup>32</sup>
  - b. Phosphorus.<sup>32</sup>
  - c. Estrogens.<sup>33, 34, 35</sup>
  - d. Saponin.<sup>36, 37</sup>
  - e. Specific antibodies.<sup>36, 38</sup>
  - f. Charcoal.<sup>9</sup>
  - g. Anterior pituitary extract.<sup>39, 40</sup>
  - h. Parathyroid extract and irradiated ergosterol.<sup>41</sup>
  - i. Myeloid and lymphoid stimulating substances<sup>42</sup>  
(See Experimental Discussion and figure 3).

This paper will be limited to a discussion of *generalized* myelofibrosis and particularly to the *primary* or idiopathic type. One case of focal myelofibrosis (fibrosis of the bone marrow with associated excessive osteosclerosis or endosteal thickening) has been included for the sake of completeness and because of the rarity of this condition. A complete discussion of this case has been published elsewhere.<sup>2</sup>

*A. Primary idiopathic generalized fibrosis of the marrow* was first termed myelofibrosis (see synonyms above) by Mettier and Rusk<sup>10</sup> in 1937.

TABLE I

Case Studies of Myelofibrosis, Both Primary and Secondary, Arranged According to the Classification Presented in the Introduction

Case No.	Name, Sex, Age, Color, Occupation	Date of Admit, Hosp. No.	Chief Complaints (on first admission) and Their Duration	Physical Findings	Laboratory Findings (Essential Findings)	Marrow Puncture Aspirations (Sternal unless otherwise indicated)	Biopsy (Site and Microscopical Diagnosis)	Treatment	Results and Remarks, also Essential Autopsy Findings (See Pathology)
Focal I. Primary (1)	P. Sil. M 35 W F—27—W. Secretary	5-0-39 6-26-39 3-17-42 BH 10205	Pain in entire right leg. Worst in right knee.—4 years.	Essentially negative.	X-ray of bones—increased density lower half of left femur and upper half of left tibia but confined to the medullary canal. Skull—Negative. Bl. Cal.—11.6. Bl. Phos.—3.9. Phosphatase—0.0. Wass.—neg.		7-1-39 Left tibia—Myelofibrosis and Myelofibrosis. 8-10-39 Exploratory laminectomy—Fibrosis of ligamentum flavum.	Sedatives and physio-therapy.	Discharged as possible anison disease—infarction of nutrient vessels to bone. Later considered Mononucleic Medullary Osteosclerosis. (See ref. 2.) 1943—Patient quite comfortable. Without pain (Oct. 1944).
II. Secondary No case study presented									
Generalized I. Primary (2)	P. Hob. M 35 W Foundry worker	11-9-43 GH 6088	Weakness—6 mo. Bone pains in feet and legs—6 mo. Refractory Anemia—6 mo. Irregular slight fever.	Pallor and possibly slight jaundice. Spleen just palpable. Few ecchymoses.	X-ray of bones—generalized demineralization and changes in spine suggesting Marrow Stump disease. MCV—100. Hematocrit—19. Liver function studies—normal. Wassermann—negative.	One attempt failed. 2nd revealed hypoplasia of marrow elements.	11-29-43 Sternum—Myelofibrosis.	Testosterone 25 mg. daily. i.m. from 12-10-43 to 1-10-44. Brewer's yeast orally. Red blood cell suspensions.	Died 1-31-44. No autopsy.
	E. Lac. F 2 W	7-8-43 GH 1510	Refractory anemia and asso. symptoms, loss of appetite and weight—6 mo. Listless. Slight, irregular fever.	Pallor. Splenomegaly—3 cm. Hepatomegaly—1 cm. Petechiae on both legs.	X-ray—long bones skull and chest—normal. MCV—87. Hematocrit—27. Bleeding time—slightly increased. Fragility—normal. Wass.—neg. Bilirubin—.1 mg. %.	Two attempts on tibia, one on femur failed. Sternum revealed hypoplasia of all elements.	8-18-43 Rt. tibia—Myelofibrosis.	Liver extract, iron and transfusions apparently failed. Testosterone 10 mg. i.m. 2X weekly started 12-10-43. Associated with oral yeast extract and conf'd until June 1944.	Is more active physically. Partial remission for the 6 mos. preceding Oct. 1 1944.
(4)	J. Lam. M 46 W Carpenter	1-13-44 GH 5437	Tiredness and weakness 4 yrs. Bone pains in legs 4 wks. Jaundice and pallor noticeable for one month.	Pallor. Spleen—8 cm. Liver—6 cm. below costal margin. No lymphadenopathy.	X-ray—increased density of all bones. Bl. Cal.—9.2. Bl. Prot.—3.3. Bl. Phosphatase—10.4 units. Bl. Plasma Prot.—5.7. Wass.—neg. Urinary estrogens—30 Mouse Units/24 hrs.	Sternal puncture—hypoplasia with atypical myeloid cells.	1-15-44 Sternum—Myelofibrosis. (See figure 2.)	Testosterone 25 mg. i.m. daily from 1-25-44 till 3-1-44. From March to Oct. 1944 received 55 red blood cell suspensions.	Clinically comfortable but suspensions required to maintain adequate red blood cell level.
(5)	R. Mar. F 40 W Housewife	6-8-43 GH 294	Refractory anemia and associated symptoms (tiredness, weakness, dizziness)—1 year. Slight irregular fever.	Pallor. Splenomegaly—4 cm. Hepatomegaly—3 cm. No lymphadenopathy.	X-ray—long bones show marked thickening. Sigmoidal diverticuli. Bl. uric acid, Cholesterol, Cal. Phosphorus, Phosphatase, Plasma Prot., Prothrombin, Bilirubin—Normal. Fragility—normal. BMR—+7. Gastric analysis—normal. Wass.—negative.	Fourth attempt on sternum obtained some fluid which revealed a few normoblasts.	6-28-43 Sternum—Myelofibrosis	Iron, liver extract, yeast, and transfusions were given. None effective.	Patient has remained unchanged chemically, but requires transfusions and red blood cell suspensions. Clinically comfortable Oct. 1944.

TABLE I—Continued

Case No.	Name, Sex, Age, Color, Occupation	Date of Admis. Hosp. No.	Chief Complaints (on first admission) and Their Duration	Physical Findings	Laboratory Findings (Essential Findings)	Marrow Puncture Aspirations (Sternal unless otherwise indicated)	Biopsy (Site and Microscopical Diagnosis)	Treatment	Results and Remarks, also Essential Autopsy Findings (See Pathology)
(6)	F. Tic. M 50 W Piano tuner	3-11-43 FH 10183	Refractory anemia and associated symptoms—3 yr. Deep bone pains in feet and ankles—4 yrs. Progressively worse. Cordelo taken—1 yr. Irregular slight fever. Weakness and lassitude.	Slight pallor—undernourished. Spleen just palpable. Liver—normal size. Lymph nodes—inguinalis slightly enlarged. Tenderness over tibial crests.	X-ray—Ribs, pelvis, femurs—increased density suggestive of Paget's disease. Bl. Phosphatase, Calcium and Phosphorus, Bilirubin—normal. Prothrombin 70%. Wass., EKG, Urinalysis—neg. BMR +9. Oscillometric tests (with histamine)—normal. Hematoerit 24. Bleeding Time—slightly increased.	Three attempts to obtain marrow fluid from sternum were unsuccessful.	4-7-43 Sternum—Myelofibrosis. (See figure 2.)	Testosterone—25 mg. daily, i.m. from 4-9-43 to 4-30-43, then 2X weekly until 6-3-43. Red blood cell suspensions also.	By 7-7-43 patient had no leg pains, stopped use of codeine, and returned to work. 12-17-43 patient killed by bus. (See discussion.) A piece of calvarium was secured and "although there was some replacement of the marrow by fibrous tissue" it had nearly a normal amount of hemopoietic elements. (See figure 2.)
II. Secondary a. Leukemia (7)	B. Bren. M 40 W Ship Fitter	11-26-42 FH 6553 1-3-43 FH 7835 6-10-43 GH 391 10-1-43 GH 4020	Refractory anemia—2 yrs. Bone pains in thighs, knees and lower back—2 yrs. Slight irregular fever, and occasional chills. Weakness. Sharp pain occasionally in upper left quad. (Spleen infarct) for 6 mos.	Spleen extends 10 cm. below left costal margin. Liver—1 cm. No lymphadenopathy. Pallor.	(Elsewhere in October 1939) X-ray of pelvis—appr. normal. W.B.C. 14-15,000. Sternal puncture—normal. Spinal fluid—88 mg. protein. Urine—casts and albumin. (Lab. Findings—Jefferson Hospital) X-ray of bones—incr. density of all except skull. Blood calcium plus, phosphatase, urea nitrogen, bilirubin, Wass., sugar—normal. Urea clearance—30%. Spinal fluid—84 mg. protein. Prothrombin—30%. MCV—77; Hematocrit—27. Spleenic puncture—extramedullary neutropoiesis. (See figure 1, D.) Testes enlarged—leukemic infiltration(?). Urinalysis neg. until last 6 mo. of life. Then persistent albuminuria and urea clearance of 25%.	Marrow fluid obtained by sternal puncture revealed hypoplasia of all elements.	12-9-42 Sternum—Myelofibrosis. (See figure 1.)	Because the spleen and liver had enlarged so markedly and had so adequately compensated for marrow replacement, testosterone was not started until 10-19-43. He received 25 mg. daily until death 11-6-43. The prothrombin remained consistently below normal throughout in spite of vitamin K administration. The patient received 100 r of x-ray on 11-4-43 and 11-5-43 preceding his sudden death on 11-6-43, in an attempt to control the progress of a boil (Staph. aureus) on his forehead.	Died 11-6-43. Myelofibrosis secondary to myeloid leukemia. Marked extramedullary hemopoiesis in liver, spleen, lymph nodes and kidneys associated with leukemic infiltrations. The foci contained megakaryocytes in abnormal preponderance.
b. Hodgkin's disease (8)	L. Dun. F 43 W Housewife	9-23-43 GH 4312 Third Admis.	Weakness, loss of weight, fever, generalized lymphadenopathy, adenopathy, aching bone pains (thighs and back). Abdominal soreness. Duration of symptoms—four years.	Pallor. Generalized lymphadenopathy. Liver and spleen both 10 cm. below costal margin.	X-ray—pelvis and femurs—negative. Persistent albuminuria. Severe anemia, usually a leukopenia associated with occasional normoblasts and myelocytes. Liver function tests normal.	Hypoplasia of all marrow elements.	3 lymph node biopsies, 1st admis. (1940) Hodgkin's 2nd admis (1941) Lymphosarcoma 3rd admis. (1943, Hodgkin's	X-ray therapy—Patient had received 2000 r units of x-ray during 2 years preceding death. Transfusions.	Died 12-12-43. Autopsy findings: Reticulum cell sarcoma involving lymph nodes, spleen, liver, and bone marrow—associated with myelofibrosis. Similar case described in reference no. 26.



TABLE I—Continued

Case No.	Name, Sex, Age, Color, Occupation	Date of Admis. Hosp. No.	Chief Complaints (on first admission) and Their Duration	Physical Findings	Laboratory Findings (Essential Findings)	Marrow Puncture Aspirations (Sternal unless otherwise indicated)	Biopsy (Site and Microscopical Diagnosis)	Treatment	Results and Remarks, also Essential Autopsy Findings (See Pathology)
c. Carcinoma of the stomach (9)	E. Kin. M 31 W Aniline dye finisher	4-26-40 CH 10265	Epigastric pains—15 years. Nausea and vomiting. Weakness. Weight loss (20 lb.) 1 mo. Dark stools.	Pallor. Jaundice. Rt. rectus scar—gastrostomy 1937. Spleen and liver 2-3 cm. below costal margin.	Gastroscopic exam.—malignant lesion found. Blood in stools. Prothrombin consistently low. No x-ray exam. of osseous system.	Hypoplasia of all marrow elements.		Patient received over 10,000 c.c. of blood.	Died 5-15-40. Adeno-carcinoma of stomach. Myelofibrosis—secondary to osseous metastases. Similar case described in reference No. 58. (See figure 3.)
d. Carcinoma of the prostate (10)	A. But. M 50 B Laborer in coal yard. Worked 1 year in lead plant	7-3-43 GH 1308	Backache—5 wks. Chills—1 mo. Wt. loss (35 lb.)—2 mo. Occasional blood in urine—1 year.	Edema of eyelids. Uremic odor in breath. Liver—5 cm. below costal margin.	X-ray—increased density of vertebrae and pelvis suggestive of Paget's disease or metastatic lesion. Skull-negative. E.U.N. 70-130. Cal.—9.0. Phos.—4.4. Phosphatase—3.2. Wass.—negative.		Trans-urethral resection made elsewhere—Prostatic carcinoma	Patient received 4 transfusions.	Died 8-20-43. Carcinoma of prostate. Myelofibrosis—secondary to metastases of prostatic carcinoma. (Ebonized bone.) Purulent cystitis and pyelo-nephritis. (See figure 3.)
Same (11)	H. Chu. M 77 W Traveling salesman	5-9-41 DH 11050	Chills and fever—8 weeks. Loss of weight—15 lbs. in 8 weeks.	Slightly enlarged spleen. Enlarged left kidney. Auricular fibrillation. Enlarged, hard prostate.	X-ray—increased density of vertebrae and pelvis characteristic of Paget's disease. No skull x-ray made. N.P.N.—44. Albuminuria, RBC, WBC in urine. Wass.—negative.			Transfusions.	Died 5-12-41. Adeno-carcinoma of prostate. Myelofibrosis—secondary to metastases of prostatic carcinoma. Occlusion of left ureter by renal calculus, associated with pyelo-nephritis and intercapillary glomerulosclerosis.
Same (12)	A. Zit. M 60 W Gardener	4-24-41 DH 11358	Generalized aches in bones—2 mo. Mainly backache. Chills—4 mo.	Very obese. Dehydrated. Rales in bases of both lungs.	X-ray—increased irregular density in lumbar and lower thoracic vertebrae suggestive of Paget's disease. No skull x-ray. N.P.N.—80. Albuminuria. Wass.—neg.			Transfusions.	Died 5-6-41. Carcinoma of prostate. Myelofibrosis—secondary to metastases of prostatic carcinoma. Focal osteomyelitis of ribs. Bronchopneumonia.
e. Fibrosarcoma of marrow (13)	C. Smi. M 10 W School-boy	8-21-35 Elsewhere	Bone pain in neck—1 year. Bone pain in legs—3 mo. Swelling of knees, ankles, elbows, fingers—2 months. Pallor and nose-bleeds—2 mo.	Pallor. Appeared chronically ill. Spleen, liver and nodes—normal. Atrophy of most muscles.	X-ray—evidence of both an osteolytic and osteoplastic process in vertebrae and long bones, associated with periostitis. Skull—neg. Wass. NPN, Cholesterol, Calcium, Phosphorus, BMR, Urine, Bence-Jones Proteinemia, Undulant Fever Agglutination, etc.—negative or normal. MCV—47; Hematocrit—19.	Hypoplasia of all marrow elements.	Sternum—Myelofibrosarcoma	Transfusions.	Died 1-11-37. Myelofibrosarcoma of vertebrae, ribs, sternum and femur. Multiple tiny metastases in kidney. Liver, thyroid, lungs, heart, lymph nodes—negative. Similar case described in reference No. 71. (See figure 3.)

The first cases of myelofibrosis were described by Heuch<sup>43</sup> of Heidelberg, Germany, in 1879. In the United States the first case was described by Donhauser<sup>44</sup> of Philadelphia in 1908; later other cases were presented by Ballin and Morse<sup>45</sup> in 1927 and by Chapman<sup>46</sup> and Stephens and Bredeck<sup>47</sup> in 1933. There are probably less than 200 cases described in the world's literature.

*Clinically, idiopathic primary generalized myelofibrosis* is usually characterized by slowly progressive weakness, splenomegaly, bone pains and refractory anemia<sup>11</sup> (table 1). The latter is usually associated with thrombocytopenia, leukopenia and the presence of a small percentage of immature (or primitive) red and white blood cells in the peripheral blood stream (table 2). From an anatomico-pathological standpoint such peripheral blood findings are given the term "myelophthitic anemia" (first used apparently at the beginning of the century by Pappenheim to indicate a wasting or weakness of the bone marrow<sup>48</sup>), but from a clinico-pathological standpoint the term "leuko-erythroblastic anemia" has been used by Vaughn<sup>49</sup> since 1934 to indicate "any widespread invasion of red marrow by tumor, proliferating leukocytes, fibrosis or bony tissue."<sup>50, 21</sup> Since then many authors<sup>10, 11, 16, 18</sup> have pointed out that myelofibrosis may be primary or secondary to encroachment upon the marrow cavity by cells, either cancerous, metabolic (Gaucher's disease, etc.), fibroblastic or bone (cortical bone cells as in osteopetrosis, or endosteal bone cells as in myelosclerosis). *Roentgenologically*, there may or may not be osteoplastic or osteolytic changes<sup>11</sup> which are dependent upon the extent of the myelofibrosis or associated myelosclerosis. *Pathologically*, in some cases it may be difficult to determine whether myelofibrosis or myelosclerosis is the initial process. However, fundamentally it is the marrow changes that cause the anemia and ultimate death of the patient and not the bone changes per se. Of course the amount of compensatory extramedullary hematopoietic enlargement of the spleen, liver and lymph nodes usually depends upon the amount of red marrow replaced by fibrosis. The fatty marrow of the extremities usually remains fatty. In a few cases<sup>51, 52, 53, 54, 55</sup> myelofibrosis has been described in association with gelatinous or fatty changes of the marrow. (Such features may depend upon the time element as brought out experimentally by the ligation of the nutrient vessel of a femur of a rabbit.<sup>8</sup> Four to 14 days after ligation, the marrow becomes necrotic, later gelatinous.) A positive *diagnosis* of myelofibrosis can only be made after microscopic examination of a biopsied specimen of marrow (preferably from sites of red marrow, as sternum, rib, etc.), although failure to aspirate marrow fluid through a sternal puncture needle should make the clinician suspicious of the disease.<sup>11, 16, 20, 47</sup> In the *treatment* of generalized primary myelofibrosis obviously radiotherapy and splenectomy are contraindicated,<sup>11, 12, 18, 26, 53, 57</sup> and transfusions are but palliative.

B. *Clinically, generalized myelofibrosis secondary to the various diseases*

TABLE II

Findings in Peripheral Blood of Cases with Primary or Secondary Myelofibrosis

	Name, No. and Date	Hgb %	R.B.C. in Millions	W.B.C. in Thousands	Plate. in Thousands	Normoblasts (per 100 W.B.C.)	Polv. %	Myelocytes %	Myeloblasts %	Eos. %	Baso. %	Lymph. %	Mono. %
A. Focal	I. Primary	82	3.9	8.7									
		78	4.5	11.6			65			2		20	13
							63			3		33	1
II. Secondary		No cases presented											
B. Generalized	I. Primary	41	1.9	2.5	28	2	22	1				70	5
		83	4.4	2.2	42	1	24					62	14
		51	2.8	2.9	10	2	42	2				36	20
		21	1.7	4.9	12	1	44	3				44	8
		39	2.4	4.7	76	1	37	1		1		58	3
		46	2.2	4.5	52	2	41					57	2
		24	1.6	6.0			29	2		1		63	5
		26	1.6	6.3	40	8	30	1		1		57	2
		25	1.5	5.0		7	34	14	5	1	4	26	16
		52	2.6	4.1	40	2	40	14	1		6	27	12
		54	2.3	1.6		6	60			2		31	7
		50	2.4	1.9	156	3	63	1	1			30	5
		60	2.6	2.8			52					41	7
		44	2.8	2.3			52					35	13
		49	2.5	2.9	76	2	65		2	1		30	2
		51	2.7	2.4	12	2	37	12	9		1	21	10
		47	2.5	4.4	56	12	60		6			19	4
		61	3.6	6.0			74					22	4
II. Secondary													
a. Leukemia													
		55	3.5	15.8	600	2	41	24	2		1	21	13
		47	2.8	13.0	814	4	46	19	8		6	18	3
		43	2.4	14.4	800	8	45	20	9		12	8	6
		44	2.2	20.4	1,150	4	32	29	13	1	8	14	13
		68	3.8	12.1	424	1	42	17	22	6	2	9	1
b. Hodgkin's disease													
		39	2.8	10.0			78			3	1	12	6
		63	4.0	10.2	60	3	81	1		2	1	7	5
		74	3.9	1.3			71					13	16
c. Carcinoma of the stomach													
		28	1.3	9.1	248	7	67	4		1		28	
		20	1.0	8.6	204	11	61	11		2		26	
d. Carcinoma of the prostate													
		45	2.3	7.0		1	74	1		6		12	6
		42	2.4	8.2		8	75	1		1	1	22	1
		55	2.9	20.0			85	2				11	2
		52	3.2	6.2		5	75	2		1		15	2
e. Fibrosarcoma of bone marrow													
		60	4.0	7.1	70	2	46	11	6	1		32	4
		42	2.4	2.2	60	4	42	6	4	2		44	2

\* After administrations of transfusions.

£ After administrations of red blood cell suspensions.

! After administrations of testosterone.

Red blood cell suspensions consist of 250 c.c. of packed red blood cells, and 250 c.c. of equal amounts of isotonic saline and isotonic glucose.

mentioned above in the introduction is characterized, of course, by the disease processes responsible for or associated with the fibrosis of the marrow. In table 1 there are listed cases of myelofibrosis secondary to Hodgkin's disease and to neoplasms of the stomach, prostate and bone marrow. The refractory type of anemia, myelophthisic or leuko-erythroblastic, is noted in these cases as in those with primary myelofibrosis. *Roentgenographic* evidence of osteolytic or osteoplastic changes may or may not be present; and the radiologic changes may appear late in the course of the disease.<sup>58</sup> *Pathologically*, fibrosis of the marrow (biopsy) and extramedullary hematopoiesis (enlarged spleen and liver) can be noted. The extent of the latter usually depends upon the amount of marrow that has been replaced by the original process and the secondary myelofibrosis or myelosclerosis. The *treatment* depends upon the process which causes or is associated with the fibrosis of the marrow, or upon the symptoms produced. In cancer of the breast or prostate, etc., with osseous metastases which cause bone pain, roentgen-radiation is indicated.<sup>58, 59</sup> Other symptomatic treatment is but palliative.

*C. Pathology.* A discussion of the changes observed in the biopsy and autopsy specimens of these cases of generalized myelofibrosis, both primary and secondary, follows, and the essential pathological findings in each case are listed in the accompanying tables (table 3 A and table 3 B). Since the lesions are fundamentally the same in all cases, a distinction between the primary (or idiopathic) and secondary forms of generalized myelofibrosis is not necessary. The changes may be conveniently considered from the following aspects: (1) endosteal bone, (2) bone marrow, and (3) extramedullary hematopoiesis.

(1) *Bone changes.* There may be a diffuse or focal proliferation of endosteal bone. Osteoblasts are usually present. Sometimes they are very large, active and surround almost every spicule of bone, whereas at other times they are greatly attenuated and sparse. Occasionally there are definite underlying zones of light pink staining osteoid tissue which are either sharply demarcated from the subjacent bone or merge gradually with it. Usually, however, the osteoid tissue is minimal or absent and spicules are composed entirely of osseous tissue. These are many times the normal thickness, deep pink staining and most often sclerotic. The lacunae ordinarily are less numerous than normal and the bone is either irregularly lamellated or shows no lamellation whatever. When lamellae are still discernible the separating bluish stained fibrils when present are very ill defined, hazy in appearance, and usually short. Neither do they have the concentric appearance ordinarily seen, nor are they distinct enough to be confused with the mosaic structure so constantly observed in osteitis deformans. There is always a conspicuous paucity, or a complete absence of osteoclasts. Those that are found, however, are of the ordinary multinucleated variety.

(2) *Changes in the marrow* may occur either separately or in association with myelosclerosis. Some cases apparently start as a diffuse or focal hypo-

plasia of all the marrow elements. There then appears a gradual increase in the underlying reticulum, first as a fine fibrillary and even somewhat myxomatous connective tissue, but later there is a gradual increase of collagen until the entire structure becomes densely fibrotic. The cellularity of the fibrous tissue varies. Sometimes the nuclei are very large, swollen and numerous and seem to blend intimately with the adjoining osteoblasts, whereas at other times they are small and sparse. Early in the process the vessels are fairly numerous and thin walled. Later they are inconspicuous. Scattered between the fibrous tissue strands there are present

TABLE IIIA  
Bone Changes in Biopsied and Autopsied Specimens

	Case No. and Name	Bones Examined	Myelo-sclerosis	Myelo-fibrosis	Remaining Hematopoiesis	Megakary-ocytes	Tumor Metastases
A. Focal							
I. Primary	1. P. S.	Tibia (Biop.)	Severe	Moderate	Very occasional foci	None	None
II. Secondary	No cases presented						
B. Generalized							
I. Primary	2. P. H.	Stern. (Biop.)	Extensive	Diffuse; Early	None	Normal	None
	3. E. L.	Stern. (Biop.)	Moderate	Diffuse; Early	Focal; Hyperplastic	Normal	None
	4. J. L.	Stern. (Biop.)	Moderate	Moderate	Focal; Hyperplastic	Increased	None
	5. R. M.	Stern. (Biop.)	Extensive	Diffuse; Early	Focal	Normal	None
	6. F. T.	Stern. (Biop.)	Extensive	Diffuse; Severe	Focal; Hyperplastic	Greatly increased	None
		Skull (Autop.)	Severe	Slight	Almost normal	None	None
II. Secondary							
a. Leukemia	7. B. B.	Stern (Biop.)	Severe	Diffuse; Extensive	Focal; Hyperplastic	Greatly increased	None
		Ribs } (Autop.) Stern. } L. Vert. }	Severe	Diffuse; Extensive	Focal; Hyperplastic	Greatly increased	None
b. Hodgkin's disease	8. L. D.	Ribs } (Autop.) Stern. } D. and L. Vert. }	None	Diffuse; Very early	Diffuse; Hypoplastic	Normal	Large necrotic masses of Hodgkin's tissue
c. Carcinoma of the stomach	9. E. K.	D. and L. Vert. (Autop.)	None	Diffuse; Early and late	Consid. necrosis; Very occ. foci; Hyperplastic	Normal	Only few cells from carcinoma of the stomach
d. Carcinoma of prostate	10. A. B.	Skull } (Autop.) Stern. } Ribs } D. and L. Vert. }	Severe	Focal areas of extensive fibrosis	None recognized	None	Diffuse from carcinoma of the prostate
"	11. H. C.	D. and L. Vert. (Autop.)	Extensive	Diffuse; Early and late	Islands of normal	Normal	None, but patient had carcinoma of prostate
"	12. A. Z.	Ribs } (Autop.) L. Vert. }	Ribs—Slight Vert.—None	Diffuse; Early and late	Few scattered foci	Normal	Few cells from carcinoma of the prostate
e. Fibro-sarcoma of bone marrow	13. C. S.	Stern. (Biop.)	Moderate	Diffuse	Focal but often necrotic	Decreased	Sheets of myelofibro-sarcoma cells
		Ribs } (Autop.) Stern. } Vert. }	Moderate	Diffuse	Focal but often necrotic	Decreased	

foci of regular or greatly hyperplastic hematopoiesis which usually contain both myelogenous and erythrocytic cells. Although megakaryocytes ordinarily are not increased sometimes they may be so numerous as to overshadow all other elements. In some cases there is apparently no preliminary hypoplasia of the marrow, but instead focal necrosis of the blood forming elements with varying amounts of hemorrhagic extravasation. Although these regressive changes most frequently occur at the site of metastatic tumors, the latter do not necessarily evoke such a reaction, for occasionally there are only a few nests of metastatic tumor cells, no necrosis, and a dif-

TABLE IIIB  
Extramedullary Hemopoiesis in Autopsied Specimens

	Case No. and Name	Spleen	Liver	Lymph Nodes	Lungs	Kidney
B. Generalized						
II. Secondary						
a. Leukemia	7. B. B.	Wt. 2,650 gm. Diffuse hemato- poiesis. Numer- ous megakary- ocytes	Wt. 4,840 gm. Diffuse hemato- poiesis. Numer- ous megakary- ocytes	Diffuse hemato- poiesis. Numer- ous megakary- ocytes	Focal hemato- poiesis with scattered megakaryocytes	Focal hemato- poiesis. Numerous megakaryocytes
b. Hodgkin's disease	8. L. D.	Wt. 550 gm. No hemato- poiesis. Hemosiderosis	Wt. 1,860 gm. No hemato- poiesis. Hemosiderosis	None	None	None
c. Carcinoma of the stomach	9. E. K.	Wt. 670 gm. Diffuse hemato- poiesis	Wt. 2,950 gm. Diffuse hemato- poiesis	None	None	None
d. Carcinoma of the prostate	10. A. B.	Wt. 40 gm. No hemato- poiesis. Hemosiderosis	Wt. 1,630 gm. No hemato- poiesis.	None	None	None
"	11. H. C.	Wt. 350 gm. None	Wt. 1,810. None	None	None	None
"	12. A. Z.	Wt. 320 gm. Focal hemato- poiesis. Few mega- karyocytes	Wt. 2,310 gm. Diffuse hemato- poiesis. Few megakaryocytes	None	None	None
e. Fibro- sarcoma of bone marrow	13. C. S.	Wt. 70 gm. Focal hemato- poiesis	Normal size for age of patient; focal hemato- poiesis	None	None	None

fuse fibrosis which is out of all proportion to the amount of tumor tissue present.

(3) *The development of extramedullary hematopoiesis* appears to be a compensatory mechanism and entirely dependent upon the degree of myelofibrosis and myelofibrosis. In this series of seven autopsied cases there were four (nos. 7, 9, 10 and 12) in which such changes in the marrow were far advanced. In three (nos. 7, 9 and 12) of these there was unequivocal extramedullary hematopoiesis. The organs most frequently involved are the liver and spleen, but hematopoiesis may also be seen in the lymph nodes, lungs and kidneys. Grossly, the liver and spleen are almost always enlarged, and occasionally they assume huge proportions. They are invariably firmer than normal. Microscopically, foci of myelocytic and erythrocytic cells are found scattered throughout the organs. Ordinarily megakaryocytes

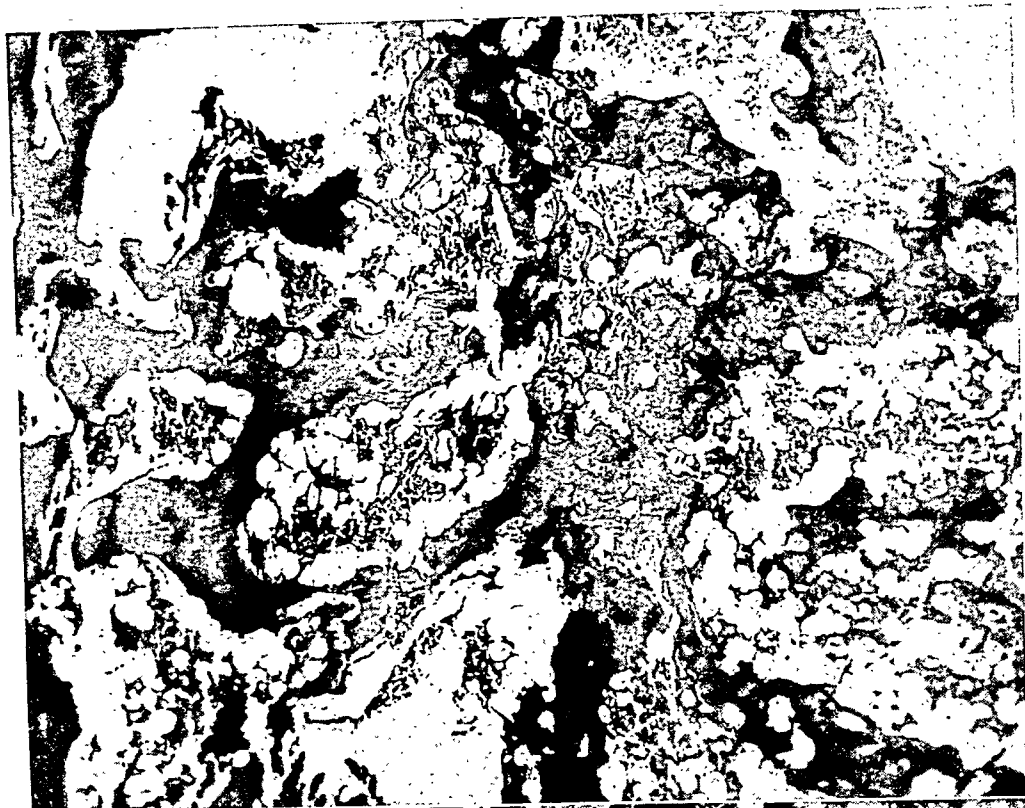
are in abeyance, but at times they may be so increased as to overshadow all other constituents, as in case 7.

## DISCUSSION

*A. Etiology.* The etiology of myelofibrosis is poorly understood, but the experimental approaches to this subject are most promising. As can be observed in the above classification (*B* II 14,) many substances can be responsible for the development of fibrosis of the bone marrow. One could assume, therefore, that myelofibrosis has many and varied causes and consequently many and varied treatments. It has been demonstrated that estrogens can be a cause of fibrosis of the bone marrow.<sup>33</sup> Since testosterone acts as an inhibitor to estrogens, testosterone can inhibit the myelofibrosis caused by excessive estrogens<sup>35</sup>; or if the preponderance of estrogens in a case of myelofibrosis were due to an inability of the liver to conjugate the estrogens, in normal quantities, one might give the vitamin B complex which would theoretically enhance the conjugating ability of the liver<sup>56</sup> and thereby overcome the progressive course of myelofibrosis. Estrogens, however, may function in a variety of ways, for in some 40 cases of prostatic carcinoma Huggins<sup>60</sup> has shown that following estrogen therapy, "in four patients extensive osseous metastases have completely disappeared to radiographic examination." (Whether these four cases had myelofibrosis secondary to the osseous metastases is unknown, because biopsies were not made.) This type of regression is possibly similar to that seen when Paget's disease reaches the healing stages. Jaffe<sup>61</sup> noted that in the healing process of Paget's disease there is a "tendency to the return of a normal appearance of both the bone and bone marrow" and "the fibrous marrow becomes replaced by more lymphoid and fatty marrow." The *mechanism* for the formation of *secondary myelofibrosis*, in patients with cancerous processes with osseous metastases and in those with Paget's disease, is probably the associated chronic occlusion of the blood vessels of the marrow (chronic infarction can be produced experimentally by the injections of carbon particles<sup>9</sup>). It is known that acute occlusion of the blood vessels to the marrow, as in caisson disease<sup>62</sup> (gas bubbles), will not cause myelofibrosis. Therefore, in the treatment of secondary myelofibrosis, one of the objectives is to inhibit or overcome chronic occlusion of the blood vessels of the marrow; another is to overcome endocrine imbalances.

Martland<sup>80</sup> has brought out one interesting feature—that irradiations of radium, thorium, and possibly other elements made radioactive artificially, administered internally, when in direct contact with bone marrow cells for long periods of time ("the third stage") ultimately cause myelofibrosis, but that irradiations of roentgenographic machines or of radium applied externally (to the skin) cause aplasia or hypoplasia of the marrow. One would expect, therefore, that the former type of irradiation is more apt to cause narrowing of the blood vessels of the marrow than the latter.

A



B

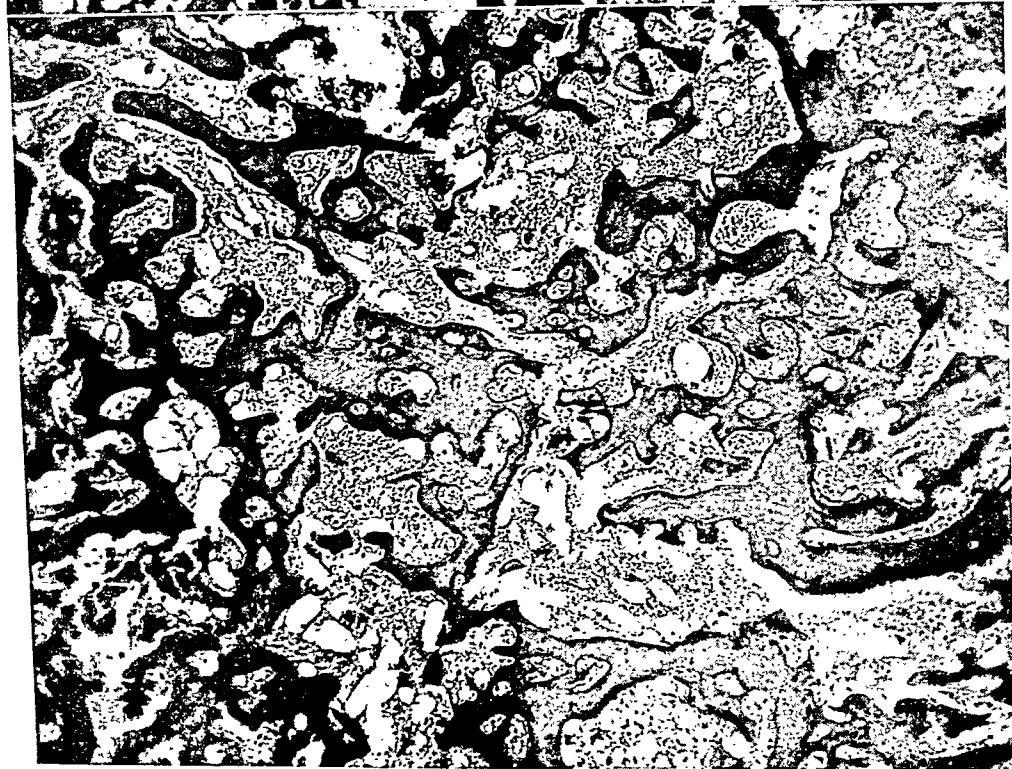


FIG. 1. (Continued on page 876.)

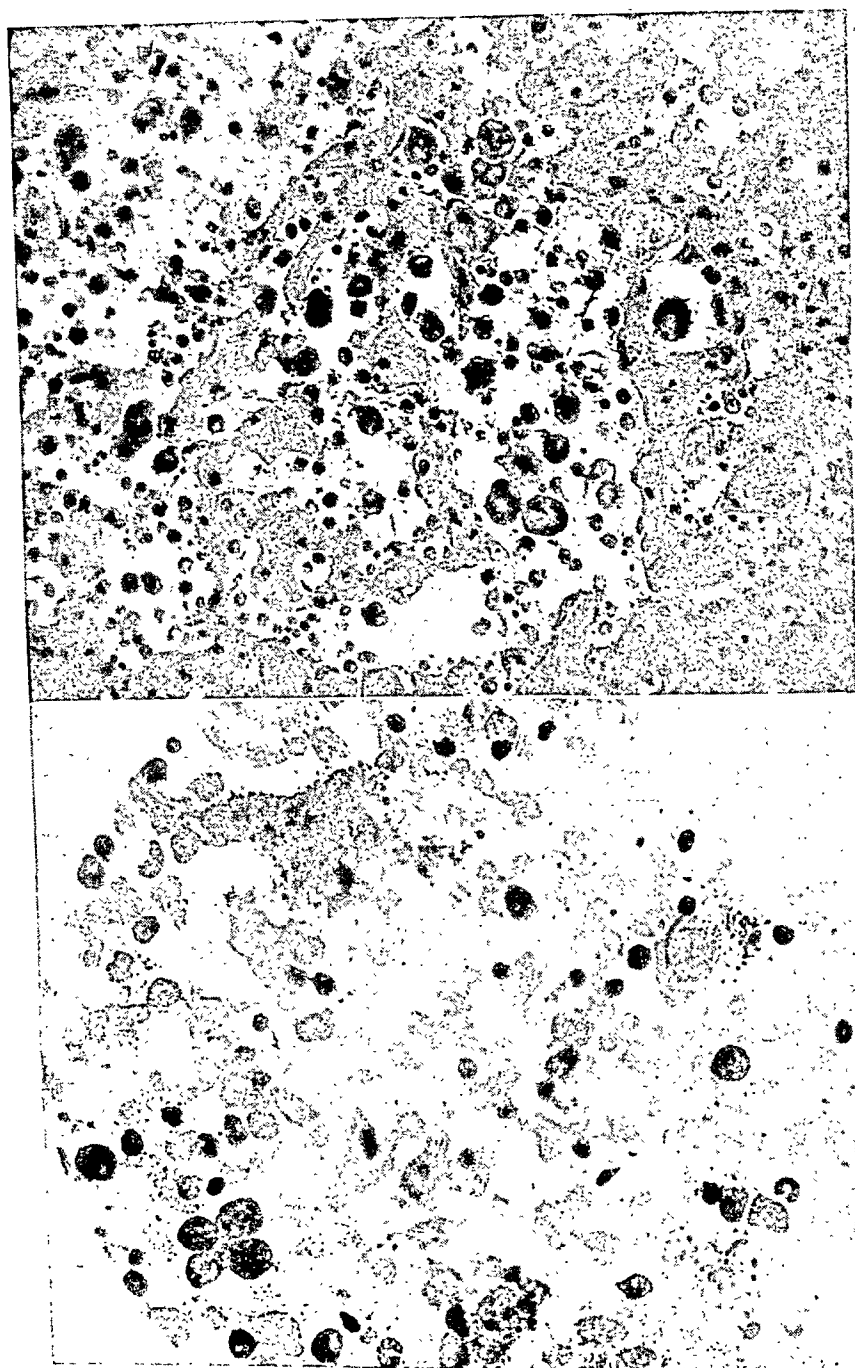




FIG. 1. (Continued on page 877.)

Curiously enough, such an apparently abstract factor as temperature plays a part in the functioning of bone marrow. Huggins et al.<sup>63</sup> showed by surgically inserting the tip of the intact tail of a rat into its own abdomen that the increased heat of the abdomen made the marrow within the tip red and active whereas the marrow within the remainder of the tail was fatty and hematopoietically inactive. One of us (L. A. E.) inserted aspirated red femoral marrow fluid of rabbits into the anterior chambers of their own eyes. The marrow quickly became yellow. Within a month (upon aspiration of the anterior chamber) the predominating cells were red cells and lymphocytes; and within two months the marrow had been replaced by bone and fibrous tissue. Lowered temperatures could have been responsible for the results. The low temperature of the marrow of the extremities may be the explanation of the clinical finding, apparently first pointed out by Piney<sup>15</sup> that metastases occur in red marrow and rarely, if ever, in fatty marrow (where temperatures are low). Whereas the blood producing ability of the marrow probably depends upon temperature, fibrosis of marrow does not. Fatty marrow and fibrous marrow are two entirely different conditions.

Bunting<sup>36</sup> and later Nettleship<sup>38</sup> produced myelofibrosis in rabbits by first injecting ether soluble extracts of rabbit marrow into guinea pigs and



D

E

FIG. 1. Case 7. A. Biopsy of sternum—showing fibrosis of marrow and myelosclerosis. B. Sternum (autopsy)—showing fibrosis of marrow and myelosclerosis. C. Roentgenogram of pelvis—showing generalized increased density of bones, also density of bones compared with density of cystoscope. D. Splenic puncture—showing extramedullary hematopoiesis, normoblasts, myelocytes, megakaryocytes, etc. E. Liver (autopsy)—showing extramedullary hematopoiesis (normoblasts, myelocytes, megakaryocytes, etc.).

then later injecting guinea pig sera which contained the marrow antibodies into other rabbits. Miller and Turner<sup>42</sup> have produced myelofibrosis in guinea pigs by the injections of an ether soluble extract of urine of patients suffering with myeloid leukemia (figure 3 D). From an embryological standpoint one might say that the three primitive layers, ectoderm, endoderm and mesoderm, have progeny which after various differentiations reach certain destinies. The first two layers ultimately are desquamated, the first exteriorly, the second internally, and the progeny of mesoderm which includes bone marrow and bone becomes fibrous tissue. Bone marrow cells or white blood cells when grown in culture tubes lose their differentiations and become fibroblastic. Miller and Turner<sup>42</sup> have demonstrated that if bone marrow cells are given the proper organizers or stimulants the normal marrow cells become either myeloid or lymphoid in character depending upon the amount of myeloid-stimulating and lymphoid-stimulating substances<sup>64</sup> present. By giving both of these substances in large quantities to guinea pigs, they have produced Hodgkin's-like tissue in the bone marrow. This tissue has much fibrosis and many megakaryocytic-appearing cells. Firket et al.,<sup>87</sup> by the injection of saponin, have also produced infiltrations of megakaryocytes in the liver, spleen, lymph nodes, etc., of rabbits and if the injections were continued over a long period of time fibrosis of marrow appeared. Therefore, it can be seen that one can experimentally produce fibrosis and megakaryocytosis of the bone marrow, a condition which has been found in man (case 7, table 1).

In summary, one can observe that many factors, such as occlusion of the blood vessels of the bone marrow, infarction of the marrow, temperature, hormones, organizers, etc., can play parts in the etiology of myelofibrosis.

*B. Treatment* (tables 1 and 4). As brought out under etiology it is possible that some cases of primary myelofibrosis may be due to excessive estrogens. Acting upon that assumption and upon the experimental work of Miller et al.,<sup>35</sup> four cases (nos. 2, 3, 4 and 6) of primary myelofibrosis and one of secondary myelofibrosis (no. 7) were given testosterone in spite of the fact that the excreted urinary hormone values (table 4 and ref. no. 67) in three of these could not be considered particularly abnormal. In the fourth, a male (no. 4, table 4), a low androgen level and a high estrogen level were noted. The use of testosterone was first brought out in a previous paper.<sup>11</sup> After testosterone was given to three of these patients (nos. 2, 4 and 6) no significant changes were noted in the urinary hormonal assays.

Case 6 responded best to the administration of testosterone. In fact, the patient had a partial remission, i.e., the anemia and leukopenia became less severe, the bone pains disappeared within two months after the initial treatment, and he returned to his work. (The remission may have been spontaneous.) The treatment was then stopped and patient remained in the remission until struck in the head by a bus and killed seven months after initial treatment. The accident occurred in another state and unfortunately

the coroner was content with an examination of the head alone to prove that cerebral hemorrhage was present. The marrow of the calvarium (figure 2 B), the only specimen obtained at autopsy, can be considered as being near normal in hematopoietic elements, although some fibrosis is present, as is true in normal individuals. In this case, as in most of the others that follow, the roentgenographic findings indicated that all the bones of the skeleton were abnormally dense.

Case 3 was given testosterone intramuscularly and yeast orally. There was an immediate rise in the reticulocyte level to 7 per cent, an increase in

TABLE IV

Urinary Hormone Assays in Cases of Primary or Secondary Generalized Myelofibrosis

	Name, No. and Date	Estrogens Free—Com- bined (Mouse units/24 hrs.)		17 Keto- steroids (mg. equiv. of andosterone/ 24 hrs.)	Androgens (Inter- national units/ 24 hrs.)	Gonadotropin (International units/24 hrs.)	Remarks
	Normal (See Ref. No. 67)	Free	Comb.				
	Men (average)	10		15	75	10	
	Women (average)	10		10	50	(Variable during menses)	
A. Focal							
I. Primary	No studies made						
II. Secondary	No studies made						
B. Generalized							
I. Primary	2. P. H. 12-10-43 1-10-44	6—* 6—	6— 6	5.5 24.0	11		Before testosterone After testosterone
	4. J. L. 1-20-44 2-7-44	6	30 22	4.5 5.5		Non-demonstrable	Before testosterone After testosterone
	5. R. M. 6-15-43	3—	3—				
	6. F. T. 4-2-43 5-6-43 7-7-43	6—	6— 6— 6—	22.5 7.2	14	Non-demonstrable Non-demonstrable	Before testosterone After testosterone After testosterone
II. Secondary							
a. Leukemia	7. B. B. 12-21-42 1-8-43 6-11-43		13— 6—	6.0 5.0 10.7	25 16	Non-demonstrable Traces	Before testosterone Before testosterone Before testosterone

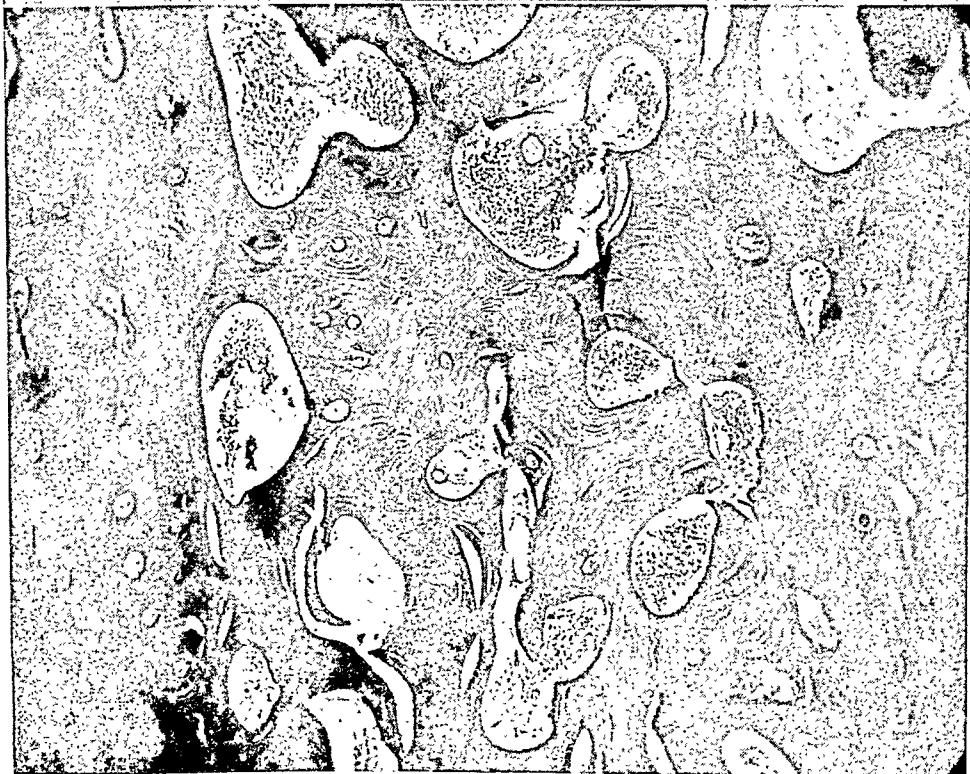
\* The minus sign (—) behind these figures means: less than.

physical activity, and a rosy color appeared in her cheeks. This patient has sisters, one two years older and another two years younger, and the mother states that the patient was much taller than either of her sisters at similar age periods. This observation would compare favorably with the experimental findings reviewed by Gardner and Pfeiffer<sup>33</sup> that excessive amounts of estrogens cause bone to lengthen abnormally rapidly and to accelerate the formation of endosteal bone. It also conforms to the work of Silberberg and Silberberg.<sup>40</sup> The majority of cases of myelofibrosis seen in children occur in females. Since receiving testosterone this patient has had some vaginal discharge, but she has not gained weight. She was also given a few

A



B



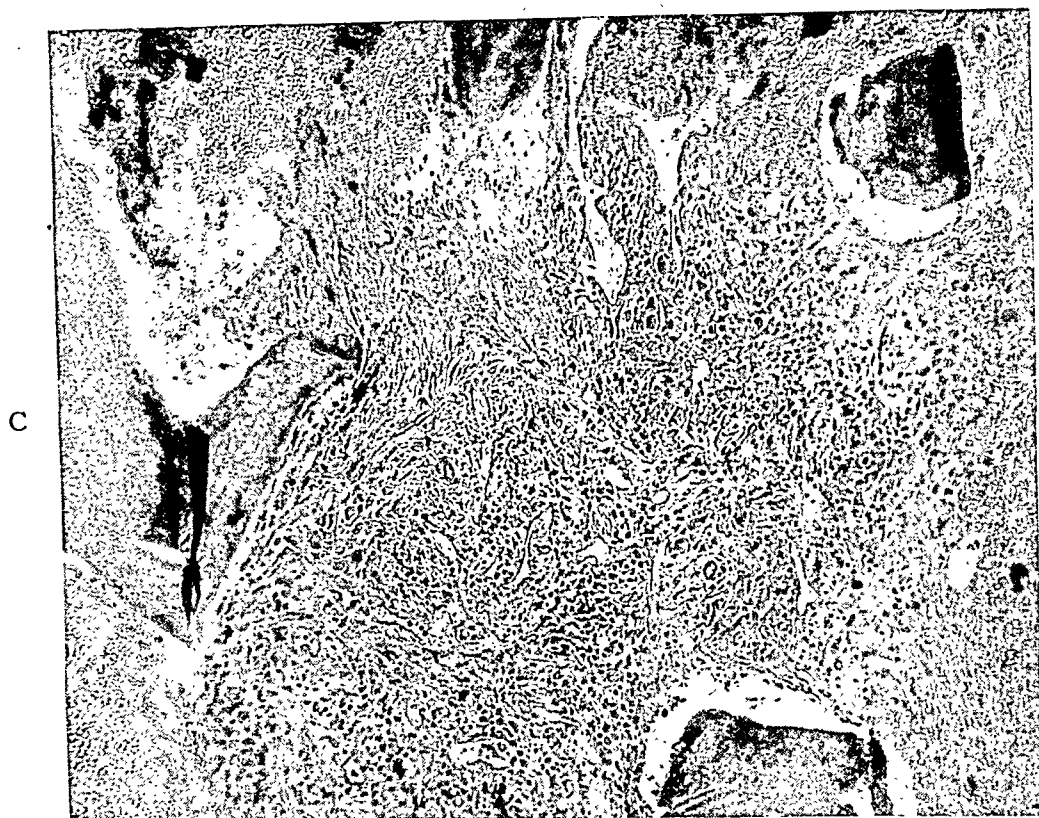


FIG. 2. Case 6. (Primary myelofibrosis.) *A.* Biopsy of sternum—showing fibrosis of marrow. *B.* Skull (autopsy)—showing regeneration of marrow presumably occurring after administration of testosterone. Case 4. (Primary myelofibrosis.) *C.* Biopsy of sternum—showing fibrosis of marrow.

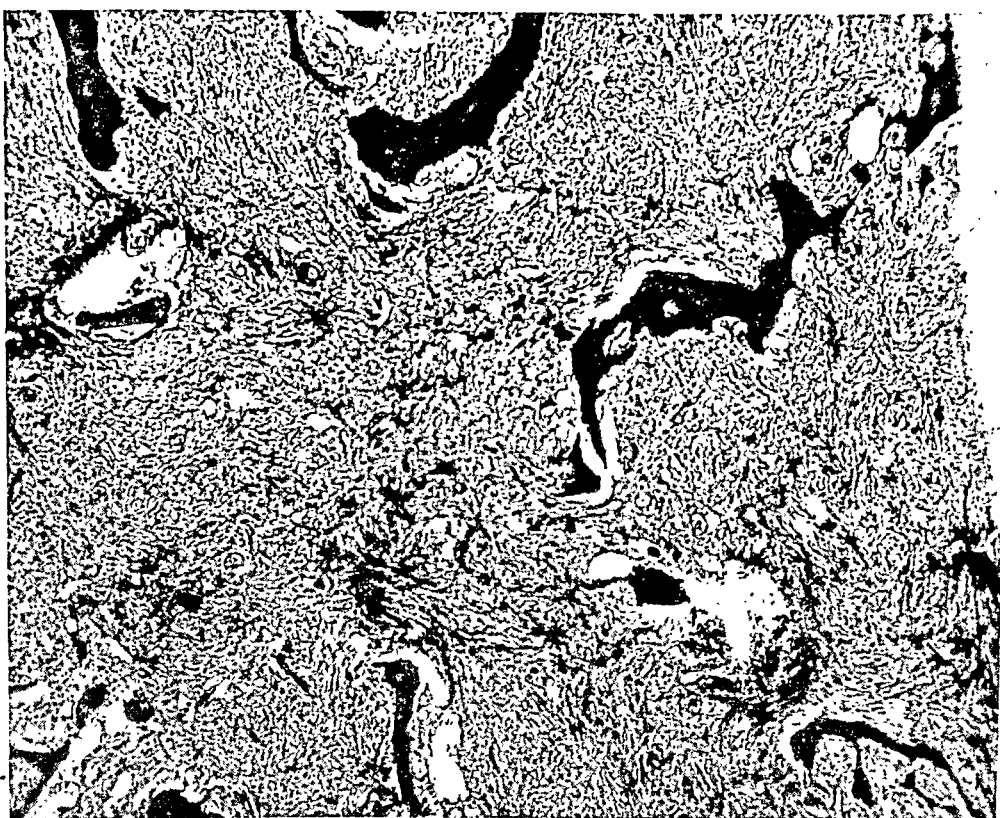
injections of adrenal cortical hormone in the hope of depressing the total number of lymphocytes in the peripheral blood stream. This patient now (Oct. 1944) is in a partial remission.

Case 2 had unusual blood findings, i.e., marked leukopenia with lymphocytosis. Testosterone apparently had no effect on the course of his disease and he died six months after the onset of his illness. A case similar to this one was described by Pinkerton.<sup>24</sup>

Case 4, like so many others, was considered pernicious anemia and was given intensive iron and liver therapy without response before being admitted to Jefferson Hospital. His response to testosterone is now being closely observed, because of the abnormally high urinary estrogen level (table 4). During the seven months preceding Oct. 1944 the patient has required 55 red blood cell suspensions. In this case the myelofibrotic process seems to continue to be progressive.

Case 7 was not given testosterone until late in the course of the disease. Because his spleen and liver had enlarged and hematopoietically compensated so adequately for the marrow which had been replaced by fibrous tissue it was felt not necessary to administer other than yeast and an occasional

A



B





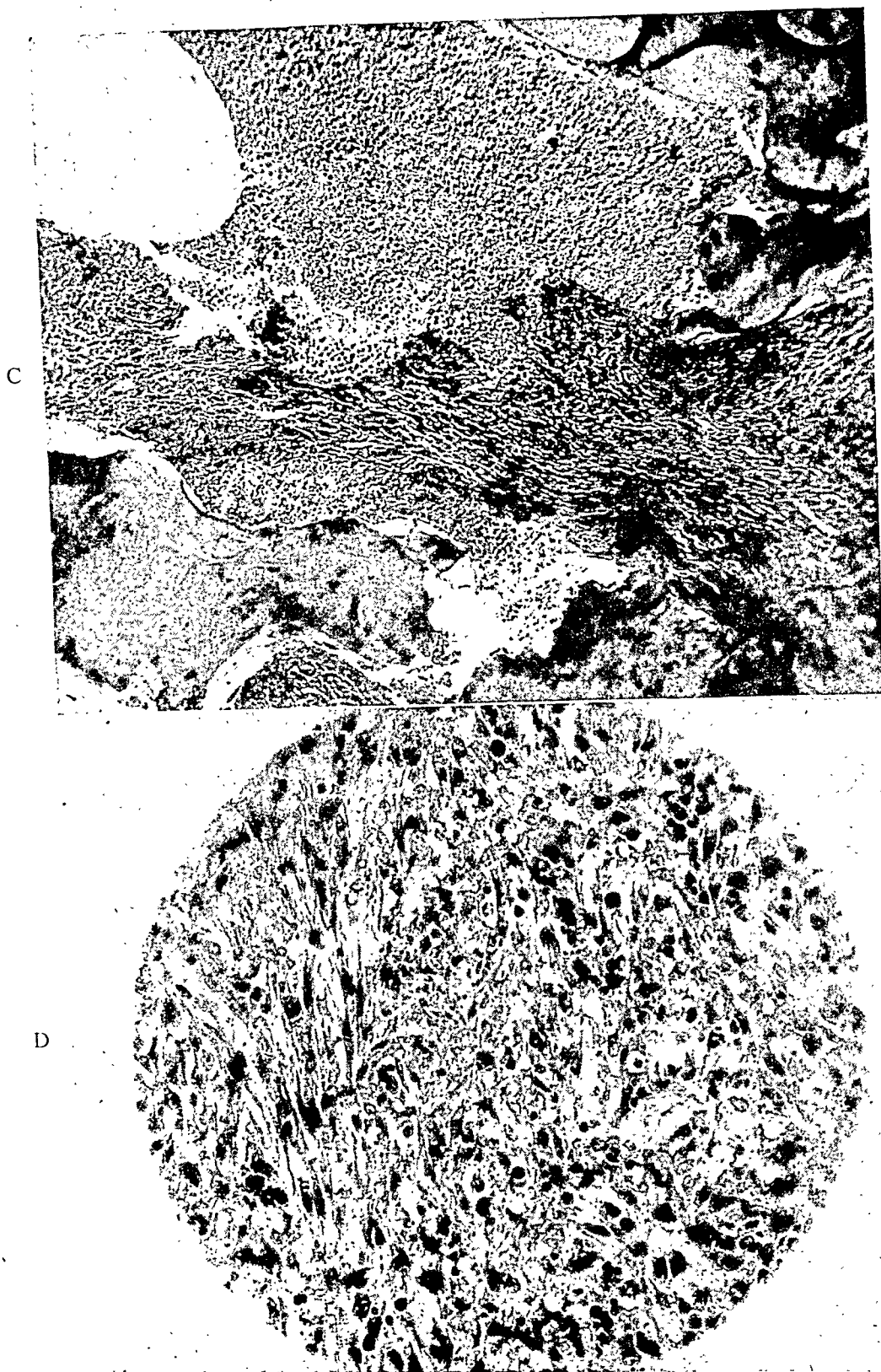


FIG. 3. *A.* Case 9. (Carcinoma of stomach with osseous metastases.) Myelofibrosis of lumbar vertebra. *B.* Case 10. (Carcinoma of prostate with osseous metastases.) Myelofibrosis of lumbar vertebra. *C.* Case 13. (Myelofibrosarcoma.) Sternal biopsy showing tumor associated with marrow necrosis and early myelofibrosis. *D.* Fibrosis of femoral marrow of guinea pig produced by injection of myeloid stimulating substance. (See discussion.)



500 c.c. suspension of red cells (he had consistently normal blood protein levels). In fact, he was not given testosterone until after a large boil developed on his forehead which could not be controlled medically or surgically and so perhaps unwisely roentgen radiation was administered. He died suddenly after the second irradiation—a total of only 200 r. A case similar to this one was described by Hickling.<sup>12</sup> Although it was difficult to decide whether this case was or was not secondary to leukemia, it probably was the latter for the following reasons.

1. Although the findings of a sternal puncture three years before death were normal, the peripheral blood findings always were characterized by a leukocytosis and thrombocytosis, both of which persisted throughout the entire course of the illness.
2. Sternal punctures performed later revealed hypoplasia of the marrow elements.
3. The sternal biopsy revealed fibrosis of marrow. Leukemic changes were not present.
4. The extramedullary hematopoietic foci obtained from the splenic puncture fluid and at autopsy were composed of not only essentially normal marrow components but also leukemic cell infiltrations.
5. The extramedullary hematopoiesis was extensive—the spleen weighed 2,650 grams, the liver weighed 4,840 grams and perhaps 20 per cent of each was made up of extramedullary hematopoiesis. Extramedullary hematopoiesis was also prominent in the kidneys, lymph nodes and lungs. The volume of active extramedullary hematopoietic foci was probably greater than the active marrow replaced by fibrosis. This probably explains the persistent leukocytosis, myelocytosis and thrombocytosis.
6. Terminally, 22 per cent of the circulating white blood cells were myeloblasts, whereas the number of white cells in the peripheral blood ranged around 20,000 per cu. mm.

It must be reemphasized at this point that testosterone was given because of the experimental evidence presented previously and because no other medication seemed to have an equally good rationale. It was given in the hope that it would inhibit the progression of the myelofibrotic process, but not to reconvert fibrous into hematopoietically active marrow. It must also be pointed out that case 5 is quite comfortable clinically without testosterone.

*C. General.* Although generalized myelofibrosis, either primary or secondary, is perhaps rather rare, it is probably much more common than is indicated by the number of published reports of these cases. One could easily suppose that many of the cases of refractory or aplastic or hypoplastic anemia are in reality cases of myelofibrosis. (However, it must be emphasized that fibrosis of the bone marrow is distinctly different from aplasia of the bone marrow; extramedullary hematopoiesis rarely, if ever, occurs in

aplastic anemia.) At most autopsies few if any specimens of marrow are obtained, because of technical difficulties, such as sawing, decalcification, etc., and limited autopsy permission. If marrow of all the bones were routinely examined, myelofibrosis would probably be found to be as common as leukemia. (At this point it must be pointed out that we are discussing only those cases in which the fibrosis of the marrow has reached the pathological level, for there are those<sup>14</sup> who feel that fibrosis of the marrow is also a normal process and that it normally precedes ossification or bone formation.) From a clinical standpoint, if sternal biopsies were carried out in all cases of refractory anemia, more cases would undoubtedly be discovered. Also, in those cases of anemia in which repeated sternal punctures are unsuccessful, sternal biopsies should always be made.<sup>11</sup> The diagnosis of myelofibrosis must be considered when the evidence of myelophthitic or leuko-erythroblastic anemia is found, i.e., when immature red cells (normoblasts or erythroblasts) and white cells (myelocytes, myeloblasts, tumor cells, etc.) are present in the peripheral blood. Bunting<sup>36</sup> in 1906 said that the appearance of such immature red cells in the circulating blood is an expression of injury to the bone marrow and that the circulating normoblasts could originate from extramedullary hematopoietic foci. Bone marrow can be injured by various cells, i.e., bone cells (Paget's disease, myelosclerosis), tumor cells (metastatic carcinoma, myeloma, etc.), metabolic cells (xanthomatosis, Gaucher's disease, etc.), leukemic cells, etc., in addition to fibroblastic cells.

Hickling<sup>12</sup> pointed out in discussing myelofibrosis that "there are certain features which are more common in these cases than in typical cases of myeloid leukemia among which are abnormal bone formation in the bone marrow cavities and the presence of large numbers of giant cells in the myeloid tissues of the organs." It would seem that he implied that the endosteal thickening caused occlusion of marrow vessels (as occurs also in Paget's disease, metastatic carcinoma, etc.) which resulted in marrow fibrosis. This, of course, brings up the question—is myelosclerosis or myelofibrosis the underlying initial process? And the question cannot be answered adequately. There are cases of myelofibrosis, however, without associated myelosclerosis.<sup>69</sup> Schiller<sup>65</sup> made the following statement—"osteosclerosis (myelosclerosis) frequently is followed by myelofibrosis; primary myelofibrosis in general is not followed by osteosclerosis." Regardless of which is the primary process it is the replacement of marrow by fibrous tissue that kills the patient suffering with the disease.

The total amount (1,200 to 1,500 grams) of marrow in the normal individual is equal in quantity to the liver; however, perhaps less than 50 per cent of the marrow is active hematopoietically. There is probably a close correlation between the amount of active marrow replaced and the degree of anemia plus the degree of extramedullary hematopoiesis in cases of myelofibrosis. The quality or immaturity of circulating blood cells may depend upon either the damaged marrow or the extramedullary hematopoietic foci;

and in a few cases of primary myelofibrosis it is sometimes difficult to disprove the presence of a preëxisting leukemia. In the former, however, the extramedullary foci have nearly normal marrow components (normoblasts, erythroblasts, megakaryocytes, myelocytes, myeloblasts and lymphocytes), whereas in leukemia the foci consist of nests of infiltrating myelocytes, myeloblasts in myeloid leukemia, or lymphoblasts in lymphoid leukemia. In other words, the definition of extramedullary hematopoiesis is a focus of normal bone marrow components situated elsewhere than within bone and attempting to produce normal circulating red and white blood cells because of destroyed marrow, whereas the definition of a leukemic infiltration is a focus of infiltrating immature white blood cells which because of their inherent reproducing capacities produce more immature white cells (either myeloid, lymphoid, monocytoid, plasmoid). Myelopoiesis, lymphopoiesis, etc. The former is a compensatory or healing process, whereas the latter is a part of the pathological leukemic process itself.<sup>65</sup> It is, however, Dr. F. R. Miller's opinion that if ever extramedullary hematopoietic foci become greater in volume and hematopoietic activity than the original marrow in the bones, one must seriously entertain the diagnosis of myeloid leukemia. In polycythemia there is probably a greater quantity of active marrow than is found in the normal individual<sup>66</sup> and according to the above opinion the process should be classified as a type of myeloid leukemia.

### CONCLUSIONS

1. Myelofibrosis may be focal or generalized and primary or secondary. Five cases of primary generalized myelofibrosis, seven cases of secondary generalized myelofibrosis, and one case of focal myelofibrosis are presented. The classification, the clinical and laboratory findings, the biopsy and autopsy findings and the treatment of these cases are presented.

2. The etiology of myelofibrosis is unknown; however, such factors as occlusion of marrow vessels, temperature, organizers and hormones may be etiological factors.

3. Testosterone was used as a therapeutic agent in four of five cases of primary generalized myelofibrosis and one of the seven cases of secondary generalized myelofibrosis. A partial remission occurred in three of the four cases of primary generalized myelofibrosis. However, it has been observed elsewhere<sup>68</sup> that in one case of myelofibrosis a remission occurred spontaneously. The results warrant further therapeutic trial of the use of testosterone for cases of primary generalized myelofibrosis.

4. Fibrosis of the marrow is probably much more common than is indicated by the number of published reports of these cases. The marrow of all cases of refractory anemia, particularly those with myelophthisic or leukoerythroblastic anemia, should be thoroughly studied before and after death.

5. Myelofibrosis is not similar to aplastic anemia. The marrow is

fibrotic in the former and fatty in the latter; extramedullary hematopoiesis exists in the former but not in the latter.

We wish to thank Dr. H. W. Jones, Dr. F. R. Miller and Dr. C. J. Bucher for valuable assistance.

## BIBLIOGRAPHY

1. (a) ALBRIGHT, F., BUTLER, A. M., HAMPTON, A. O., and SMITH, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females, *New England Jr. Med.*, 1937, ccxvi, 727.  
(b) ALBRIGHT, F., SCOVILLE, B., and SULKOWITCH, H. W.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and a gonadal dysfunction, *Endocrinology*, 1938, xxii, 411.
2. HOROWITZ, T.: Monomelic medullary osteosclerosis, *Radiology*, 1941, xxxvi, 343.
3. TURNBULL, H. M.: Studies in calcium and phosphorus metabolism in generalized diseases of bones, *Proc. Roy. Soc. Med.*, 1935, xxviii, 1619.
4. HERTZLER, A. E.: Surgical pathology of the diseases of bones, 1931, J. B. Lippincott, Philadelphia.
5. LAWFOR, R. L.: The inflammatory and toxic diseases of bone, 1926, John Wright and Sons, London.
6. FALCONER, M. A., and COPE, C. L.: Fibrous dysplasia of bone with endocrine disorders and cutaneous pigmentation (Albright's disease), *Quart. Jr. Med.*, 1942, xi, 112.
7. CURTIS, L. E., and FELLER, A. E.: Hyperparathyroidism with calcinosis and secondary to renal disease, *Ann. Int. Med.*, 1942, xvii, 1005.
8. HUGGINS, C., and WIEGE, E.: Effect on bone marrow of disruption of nutrient artery and vein, *Ann. Surg.*, 1939, cx, 940.
9. KISTLER, G. H.: Sequences of experimental infarction of the femur in rabbits, *Arch. Surg.*, 1934, xxix, 589.
10. METTIER, S. R., and RUSK, G. Y.: Fibrosis of the bone marrow (myelofibrosis) associated with a leukemoid blood picture, *Am. Jr. Path.*, 1937, xiii, 377.
11. ROSENTHAL, N., and ERF, L. A.: Clinical observations on osteopetrosis and myelofibrosis, *Arch. Int. Med.*, 1943, lxxi, 793.
12. HICKLING, R. A.: Chronic non-leukemic myeloids, *Quart. Jr. Med.*, 1937, vi, 253.
13. PARKES-WEBER, F.: Generalized osteosclerosis, *Jr. Path. and Bact.*, 1929, xxxii, 171.
14. FAIRBANK, H. A.: Increased and decreased density of bone with special reference to fibrosis of the marrow, *Brit. Jr. Surg.*, 1939, xxvii, 1.
15. RUSK, G. Y., and MILES, W. L.: Osteosclerotic anemia secondary to epidermoid carcinoma, *Am. Jr. Path.*, 1927, iii, 289.
16. METTIER, S. R.: Hematologic aspects of space consuming lesions of the bone marrow (myelophthisic anemia), *Ann. Int. Med.*, 1940, xiv, 436.
17. JARCHO, S.: Diffusely infiltrative carcinoma, *Arch. Path.*, 1936, xxii, 674.
18. THOMPSON, W. P., and ILLYNE, C. A.: Clinical and hematological picture resulting from bone marrow replacement, *Med. Clin. North Am.*, 1940, xxiv, 841.
19. VAUGHN, J., and HARRISON, C. V.: Leuco-erythroblastic anemia and myelosclerosis, *Jr. Path. and Bact.*, 1939, xlviii, 339.
20. HYNES, M.: Sternal puncture, *Lancet*, 1939, i, 1373.
21. VAUGHN, J. M.: Leuco-erythroblastic anemia, *Jr. Path. and Bact.*, 1936, xlii, 541.
22. DONHAUSER, J. L., and DE ROUVILLE, W. H.: Multiple myeloma, with special reference to soft tissue metastases, *Arch. Surg.*, 1941, xliii, 946.
23. HIRSCH, E. F.: Generalized osteosclerosis with chronic polycythemia vera, *Trans. Chicago Path. Soc.*, 1935, xiv, 204.
24. PINKERTON, H.: Aleukemic leukemia and atypical leukemoid conditions, *Arch. Path.*, 1929, vii, 567.

25. ABRAMS, H. S.: The osseous system in Hodgkin's disease, *Ann. Surg.*, 1938, cviii, 296.
26. MENDELOFF, T., and ROSENTHAL, J.: Leukocrythroblastic anemia with diffuse osteosclerosis, *Ann. Int. Med.*, 1943, xix, 518.
27. COOLEY, T. B., WITWER, E. R., and LEE, P.: Anemia in children, *Am. Jr. Dis. Child.*, 1927, xxxiv, 347.
28. GALL, E. A.: Benzene poisoning with bizarre extra-medullary hematopoiesis, *Arch. Path.*, 1938, xxv, 315.
29. LINSMAN, J. F., and McMURRAY, C. A.: Fluoride osteosclerosis from drinking water, *Radiology*, 1943, xl, 474.
30. MARTLAND, H. S.: The occurrence of malignancy in radioactive persons, *Am. Jr. Cancer*, 1931, xv, 2435.
31. MULLIGAN, R. M.: Effects of repeated small doses of roentgen rays on canine blood and bone marrow, *Proc. Soc. Exper. Med. and Biol.*, 1941, xlviii, 607.
32. LEHNERDT, F.: Phosphorsklerose und Strontiumsklerose, *Jahrb. f. Kinderh.*, 1910, lxxii, 394.
33. GARDNER, W. U., and PFEIFFER, C. A.: Influence of estrogens and androgens on the skeletal system, *Physiol. Rev.*, 1943, xxiii, 139.
34. CASTRODALE, D., BIERBAUM, O., HELWIG, E. B., and MACBRYDE, C. M.: Comparative studies of the effects of estradiol and stilbesterol upon the blood, liver and bone marrow, *Endocrinology*, 1941, xxix, 363.
35. MILLER, E. W., ORR, J. W., and PYBUS, F. C.: The effect of estrone on the mouse skeleton, *Jr. Path. and Bact.*, 1943, lv, 137.
36. BUNTING, C. H.: Experimental anemias in the rabbit, *Jr. Exper. Med.*, 1906, viii, 625.
37. FIRKET, J., and CAMPOS, E. S.: Generalized megalocaryocytic reaction to saponin poisoning, *Bull. Johns Hopkins Hosp.*, 1922, xxxiii, 271.
38. NETTLESHIP, A.: Bone-marrow changes produced by specific antibodies, *Am. Jr. Path.*, 1942, xviii, 689.
39. SILBERBERG, M., and SILBERBERG, R.: Comparison of effects of anterior pituitary hormone on skeletal tissues of young and mature guinea pigs, *Am. Jr. Path.*, 1939, xv, 547.
40. SILBERBERG, M., and SILBERBERG, R.: Growth processes in cartilage and bone subsequent to gonadectomy and administration of anterior pituitary extract of cattle in immature male and female guinea pigs, *Am. Jr. Path.*, 1939, xv, 55.
41. SELYE, H.: On the stimulation of new bone-formation with parathyroid extract and irradiated ergosterol, *Endocrinology*, 1932, xvi, 545.
42. MILLER, FRANKLIN, and TURNER, D. L.: The action of specific stimulators on the hematopoietic system, *Am. Jr. Med. Sci.*, 1943, ccvi, 143.
43. HEUCH, G.: Zwei Fälle von Leukämie mit eigenthümlichen Blut resp. Knochenmarks-befund, *Virchow's Arch. f. path. Anat.*, 1879, lxxviii, 475.
44. DONHAUSER, J. L.: The human spleen as a hematoplastic organ as exemplified in a case of splenomegaly with sclerosis of the bone marrow, *Bull. Ayer Clin. Lab.*, 1908, v, 46.
45. BALLIN, M., and MORSE, P. F.: Myelophthisic splenomegaly, *Jr. Am. Med. Assoc.*, 1927, lxxxix, 1671.
46. CHAPMAN, E. M.: Osteosclerotic anemia, *Am. Jr. Med. Sci.*, 1933, clxxxv, 171.
47. STEPHENS, D. J., and BREDECK, J. F.: Aleukemic myelosis with osteosclerosis, *Ann. Int. Med.*, 1933, vi, 1087.
48. FRANK, E.: Aleukia haemorrhagica, *Berl. klin. Wehnschr.*, 1915, lii, 961.
49. VAUGHN, J.: *The anaemias*, 1934, Oxford University Press, London.
50. MAGNER, W.: *Textbook of hematology*, 1936, Blakiston's Son and Co., Philadelphia, p. 166.
51. TAYLOR, H. E., and SMITH, R. P.: Marrow sclerosis associated with massive myeloid splenomegaly, *Arch. Path.*, 1941, xxxi, 803.

52. TUDHOPE, G. R.: Splenomegaly with myeloid transformation, *Jr. Path. and Bact.*, 1937, xliv, 99.
53. FALCONER, A. W., and RYRIE, B. J.: Report on a familial type of generalized osteosclerosis, *Med. Press*, 1937, cxcv, 12.
54. JORDAN, H. E., and SCOTT, J. K.: A case of osteosclerosis with extensive extra-medullary hemopoiesis and a leukemic blood reaction, *Arch. Path.*, 1941, xxxii, 895.
55. McMICHAEL, J., and McNEE, J. W.: Leuco-erythroblastosis, *Edinburgh Med. Jr.*, 1936, xliii, 303.
56. BISKIND, M. S., and BISKIND, G. R.: Effect of vitamin B complex deficiency on inactivation of estrone in the liver, *Endocrinology*, 1942, xxxi, 109.
57. DOWNEY, H., PALMER, M., and POWELL, L.: The origin of the megakaryocytes in the spleen and liver in a case of atypical myelosis, *Folia haemat.*, 1930, xli, 55.
58. SWENSON, P. C., and HOLZMAN, G. G.: A discussion of generalized osteosclerosis with a report of an unusual case, *Radiology*, 1938, xxxi, 333.
59. KOENIG, E. C., and CULVER, G. J.: The value of roentgen therapy in carcinomatous metastases to bone, *Radiology*, 1943, xli, 38.
60. HUGGINS, C.: A summary of endocrine effects in advanced prostatic carcinoma, *New York State Jr. Med.*, 1943, xliii, 519.
61. JAFFE, H. L.: Paget's disease of bone, *Arch. Path.*, 1933, xv, 83.
62. BELL, A. L., EDSON, G. N., and HORNICK, N.: Characteristic bone and joint changes in compressed-air workers, *Radiology*, 1942, xxxviii, 698.
63. HUGGINS, C., and BLOCKSON, B. H., JR.: Changes in outlying bone marrow accompanying a local increase of temperature within physiological limits, *Jr. Exper. Med.*, 1935, lxiv, 253.
64. TURNER, D. L., and MILLER, F. R.: The preparation of concentrates of specific substances from urine and feces in leukemia, *Jr. Biol. chem.*, 1943, cxlvii, 573.
65. SCHILLER, W.: Local myelopoiesis in myeloid leukemia, *Am. Jr. Path.*, 1943, xix, 809.
66. ERF, L. A., and JONES, H. W.: Radio-phosphorus—an agent for the satisfactory treatment of polycythemia and its associated manifestations, *Ann. Int. Med.*, 1943, xix, 587.
67. RAKOFF, A. E.: The diagnostic value of hormone assays, *Med. Clin. North Am.*, 1942, xxvi, 1915.
68. ROSENTHAL, N.: A personal communication.
69. CHURG, J., and WACHSTEIN, M.: Osteosclerosis myelofibrosis and leukemia, *Am. Jr. Med. Sci.*, 1944, ccvii, 141.
70. JACKSON, H., JR., PARKER, F., JR., and LEMON, H. M.: Agnogenic myeloid metaplasia of spleen; syndrome simulating other more definite hematologic disorders, *New Eng. Jr. Med.*, 1940, ccxxii, 985.
71. STEINER, P. E.: Multiple diffuse fibrosarcoma of bone, *Am. Jr. Path.*, 1944, xx, 877.

# CASE REPORTS

---

## SIMMONDS' DISEASE WITH THERAPEUTIC RESPONSE TO HORMONE THERAPY FOR FOUR YEARS: REPORT OF A CASE WITH NECROPSY FINDINGS \*

By WARD DARLEY, M.D., F.A.C.P., ROBERT W. GORDON, M.D., F.A.C.P., and KARL T. NEUBUERGER, M.D., *Denver, Colorado*

THE recent and exhaustive review by Escamilla and Lissner<sup>1</sup> of the literature concerning hypophyseal cachexia (Simmonds' disease) is most timely. From this review it is apparent that confusion regarding the recognition of the syndrome has been very great. The facts that out of 595 reported cases only 101 were proved pathologically and that out of the remaining 494 cases only 158 were typical clinically bear out this contention. As a result of Escamilla's and Lissner's careful analysis of the proved cases, their definition of clinical criteria should lessen the confusion in the recognition of the condition and should serve as a more reliable background for the evaluation of therapy in such cases.

Any effort at this time to discuss the literature further would be superfluous. We do feel justified, however, in reporting a pathologically proved case of pituitary cachexia, which was carefully studied and observed over a period of years and which apparently responded to the exhibition of endocrine therapy.

### CASE REPORT

The patient, a male, was treated for syphilis in 1913, at 21 years of age. In 1917 a gumma of the left testicle necessitated its removal. One year later, after a severe influenzal attack, the following symptoms gradually developed: dry atrophic skin of a peculiar lemon yellow color; loss of facial, axillary, and pubic hair with a marked thinning of the hair of the scalp and eyebrows; marked fatigability and weakness; a loss of all sexual desire and power; a hesitant, monotonous, drawling type of articulation; a marked slowing of all mental processes; a desire for extra sleep; digestive disturbances, with periods of anorexia and attacks of vomiting and diarrhea; a stooped posture and peculiar shuffling gait and, finally, a persistent anemia.

In 1920, three years after the onset of this illness, excessive thirst and polyuria developed and, after several months, seemed to be relieved and to disappear following the ingestion of large daily doses of olive oil. In 1921 a ptosis of the left upper eyelid was present for a few weeks. One year later left facial and upper extremity paralysis and numbness, together with marked headache, confusion, and aggravation of the weakness, suddenly appeared. The anemia was more marked. The serologic examinations of the blood and spinal fluid were negative. Following this upset, which gradually cleared over a period of several weeks, the condition of the patient remained as before, until 1931. At this time two teeth were removed with resulting persistent hemorrhage and aggravation of the anemia. For a time the patient was in a criti-

\* Received for publication March 11, 1943.

From the Departments of Medicine and Pathology, University of Colorado School of Medicine and Hospitals.

cal state. Subsequent improvement from this setback was slow and the patient's condition, as compared with the previous level, never was as good.\*

We first saw this patient September 24, 1936, when he was 44 years of age. He had been confined to bed for several days because of progressive weakness, dependent edema, vomiting, and somnolence. He was aroused with difficulty and was irritable and petulant whenever disturbed. Generalized pitting edema was present, most marked in the lower limbs. The skin generally was of a lemon-yellow color, dry, cool, and of a parchment-like consistency; that below the knees was covered with a weeping eczematoid eruption. Pubic, axillary, and facial hair was absent and the hair of the scalp was thin and exceedingly fine. The eyebrows were almost absent and very few eyelashes were present. The facies was expressionless and mask-like. The right pupil was larger than the left; both reacted to light and accommodation. Many of the remaining teeth were carious; the gums were retracted, congested, and bleeding. The heart sounds were distant and a soft apical systolic murmur was audible. The heart was not enlarged. The penis and scrotum were infantile. The left testicle was absent; the right was about one-fourth normal size and of abnormally soft consistency. No prostate gland could be palpated by rectal examination. Neurologic examination revealed nothing abnormal. The body weight was 136 pounds, the total temperature 97° F., the respiratory rate 14, the pulse rate 80, and the blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The hemoglobin was 12.2 grams (Sahli), the red cell count 2,850,000 and the white cell count 4,000, with 56 per cent polymorphonuclear neutrophils, 29 per cent lymphocytes, 7 per cent mononuclear cells, 6 per cent eosinophiles, and 2 per cent basophiles. The blood Wassermann reaction was negative. The fasting blood sugar was 75 mg. per 100 c.c. of blood. The bleeding and coagulation times were normal. Urinalysis revealed nothing abnormal. The basal metabolic rate was minus 35. The only abnormality revealed by the electrocardiogram was a very low voltage in the classical leads (figure 1).

Four grains of desiccated thyroid (USP), 45 grains of ferrous sulphate, and 150 units of liver extract by intramuscular injection were given daily. After three weeks the patient was very little, if any better, as was no more than to be expected, since this treatment represented much the same type of régime that had been prescribed frequently over the preceding years. On October 14, the liver was discontinued, the thyroid dosage was reduced 50 per cent, and the patient began to receive 150 units of anterior-pituitary-like hormone† intramuscularly once daily. Within one week definite improvement was apparent: the urinary output increased greatly and at the same time the edema rapidly diminished; in five days the weight dropped from 136 to 112 pounds; the mental picture improved and somnolence disappeared; the vomiting ceased and a desire for food returned; the gums stopped bleeding; the strength improved, and the patient became able to get out of bed. By the end of the week generalized superficial desquamation was marked. On October 27, the thyroid was discontinued and the pituitary substance was thence administered only every other day.

By January 18, 1937, improvement, though slow, had continued sufficiently that the dosage of pituitary substance was reduced to 150 units twice weekly. On this date the hemoglobin was 12.6 grams (Sahli) and the red cell count 4,800,000. A fractional gastric analysis gave results within normal limits. The fasting blood sugar was 70 mg. per 100 c.c. of blood. An attempted glucose tolerance test was unsuccessful because the patient was unable to retain the glucose. A routine spinal fluid examination yielded normal findings. The body weight was still 112 pounds. The yellowish pallor was little, if any, improved and the skin retained its parchment-like consistency and appearance. The hair growth was unchanged and the external

\* The clinical notes from 1920 through 1931 were taken from the case records of the late Dr. Sherman Grant Bonney.

† Squibb Follutein.



genitalia appeared in no way altered. Sexual desire and power had not returned. In every other way improvement seemed marked: the voice and facial expression were more animated; strength and energy had greatly increased, although the gait

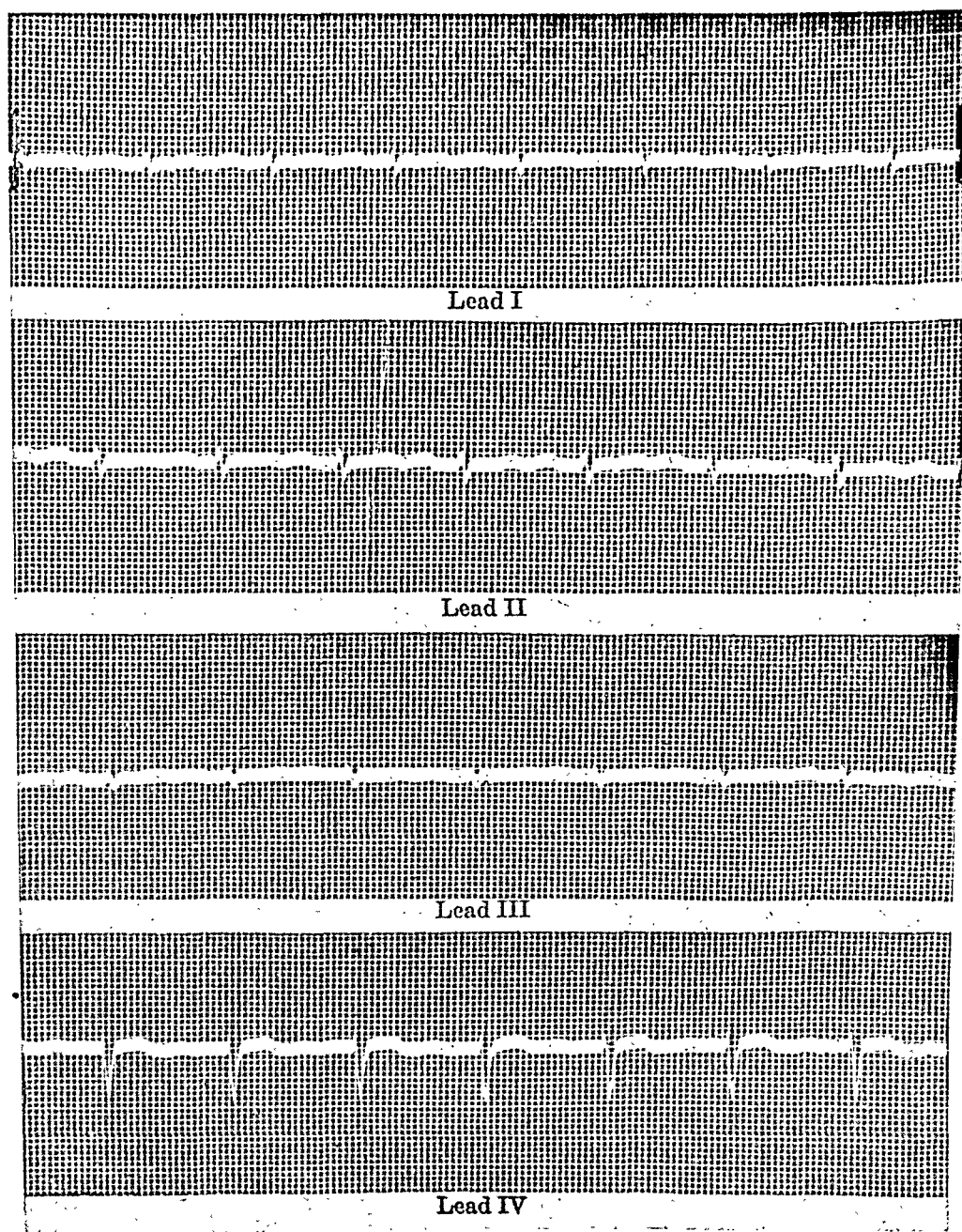


FIG. 1. Electrocardiogram—low voltage in first three leads.

was still shuffling in type; the attacks of indigestion no longer occurred and the appetite remained better; the patient's disposition was amiable, his mental processes were greatly improved, and his desire for sleep was less, with an average sleep of 12 hours

out of 24. On February 1, 1937 the patient returned to work, from which he had been absent since September 1, 1936, and which was not difficult (operation of a mechanical coin-counting device). He began to regain weight: 120 pounds was the body weight by March 1, 127 by April 1, and 133 by May 1.

In October 1937, after one year's treatment, examination indicated that the patient apparently had held his gain. He had missed no further time from work. He was still receiving two injections of pituitary-like substance a week. His weight was 130 pounds, blood pressure 110 mm. Hg systolic and 80 mm. diastolic, basal metabolic rate minus 53, hemoglobin 14 gm. (Sahli), red cell count 3,390,000, and white cell count 6,080, with a differential count of 70 per cent polymorphonuclear neutrophils, 25 per cent lymphocytes, and 5 per cent eosinophiles.

During the next three years the patient was seen only quarter-annually and seemed to be holding his own, but by January 1940 the patient and his family had become dilatory and dosage frequency had become sporadic and irregular. By May 1940 it was apparent that the patient was failing; because of weakness, somnolence and mental sluggishness he stopped work. By December 1940 he was again confined to bed; he was edematous, stuporous, and having much vomiting. In January of 1941 hospitalization was necessary. At this time, fibrillation and anasarca were present. The hemoglobin was 10 grams (Sahli), the red cell count 3,790,000 and the white cell count 5,600, with 60 per cent polymorphonuclear neutrophils, 34 per cent lymphocytes, 3 per cent large mononuclear cells, and 3 per cent eosinophiles. The blood non-protein nitrogen was 25 mg., the creatinine 1.37 mg., and the sugar 50 mg. per 100 c.c. of blood. A transfusion, digitalization, thyroid, and pituitary-like substance seemed to do very little, if any, good. Intravenous salyrgan at biweekly intervals increased the fluid-output, but marked congestive failure persisted. For the three months prior to the death of the patient on August 8, 1941, all intensive therapy was discontinued.

The necropsy was performed after embalming. The body was fairly well nourished, the skin was pale, axillary and pubic hair were missing, and the arms and legs were edematous. The panniculus adiposus measured 1 to 2 cm. in thickness. Neither pituitary nor thyroid could be discerned with the naked eye. The adrenals were scarcely half the normal size, as was the right testicle, which appeared to be diffusely fibrosed. The prostate gland was almost invisible grossly. The heart showed an old rheumatic mitral valvulitis, with a few recent verrucous vegetations; the left ventricle was dilated. The liver was atrophic and displayed several shallow scar-like indentations on the anterior surface. The pancreas was rather small and somewhat interspersed with fat and fibrous tissue. The arterial system was elastic and free from arteriosclerosis and from lesions suggesting syphilis.

Microscopically, the fibrous contents of the sella turcica failed to show any trace of pituitary tissue of either anterior or posterior lobe. There was nothing but poorly nucleated scar tissue in which were a few vascular areas containing occasional fibrocytes and round cells (figure 2).

The thyroid was extremely atrophic. Sections taken from its presumable site showed islands of lymphocytes separated by cords of connective tissue. Within these islands a few undersized thyroid follicles were arranged singly or in small groups; occasional follicles were scattered through the strands of connective tissue. The follicles were lined with flattened or low-cuboidal epithelium; their lumina were either empty or contained a small amount of pinkish colloid (figure 3).

The parathyroids, two of which were found and examined, showed well-preserved, water-clear cells and occasional oxyphilic cells. They appeared generally normal.

The adrenal cortex was atrophic and its layers were poorly demarcated. In several places fibrous strands arising from the thickened capsule overlapped and partly replaced the zona glomerulosa (figure 4). The lipid contents were poor and



FIG. 2. Obliterated pituitary.

irregularly distributed. Capillaries were dilated. The medullary tissue in some portions was greatly reduced and fibrosed; in other portions it was rather well preserved. Occasional areas, especially in the medulla, were infiltrated with lymphocytes.

The prostate consisted of small bundles of smooth muscle, interspersed with con-

nective tissue; it contained only a very few small glands, lined with low-cuboidal epithelium (figure 5).

In the testicle no normal tissue was evident. The tubules were sparse, distorted, small, and hyalinized. Several of them formed solid strands with small round nuclei in the center; most tubules, however, were anuclear. Basement membranes were thickened. The intertubular spaces were very wide and were composed of loose, poorly nucleated connective tissue. No Leydig cells were present (figure 6). The epididymis was much better preserved anatomically; the ducts, however, had very narrow lumina.

The pancreatic tissue, though interspersed with connective tissue and some fat, was, on the whole, well preserved.

Other findings included brown atrophy, splitting, and occasional basophilic degeneration of heart muscle fibers\*; brown atrophy of the liver; moderate atrophy of the gastric mucosa; hemosiderosis of the spleen, which had large Malpighian corpuscles. The remaining findings in the visceral organs were insignificant; there was no characteristic lesion of the bone marrow.

The brain showed essentially well-preserved cortical architecture. The number of nerve cells appeared about normal. Some of the cells exhibited more or less marked degenerative changes, such as paleness and vacuolation; others displayed a darkly basophilic, shrunken cytoplasm. There was little or no reaction of the supporting tissues. The thalami and the nuclei of the interbrain showed occasional ghost cells or blanched cells with faded outlines, increased wear-and-tear pigment in some of the neurons, and slight swelling of some of the oligodendroglial cells and astrocytes. These changes, altogether not conspicuous, were scattered over the centers mentioned above and were not accentuated in any one specific gray nucleus. "Senile" plaques and fibrillary alteration were absent (figure 7).

Escamilla and Lisser conclude from their review that Simmonds' disease is characterized by four cardinal signs: weight loss, asthenia, impotence, and low metabolic rate. It is difficult to determine the true significance of the varying weights in this patient. His average weight in health had been 140 pounds; between the onset of his illness and the time he first came to us, the weight had varied between 130 and 135 pounds. When the patient was first examined by us, however, he was very edematous; he rapidly lost 24 pounds as a result of the diuresis which followed the institution of therapy: the resultant 112 pounds in all probability represented his true weight. The low gain which subsequently occurred was, in all probability, the result of improving general condition. Asthenia was a marked feature in the case, particularly before therapy was started, and also later when treatment was apparently inadequate. The patient lost all sexual desire and power soon after the onset of his symptoms. The initial basal metabolic reading was minus 35. It is of interest that one year later, after clinical improvement had been so marked, the rate was minus 53.

Many other findings peculiar to the syndrome of pituitary cachexia were manifest in our case. Apathy, dullness, and drowsiness, although variable in degree, were always prominent. The body surface always felt abnormally cool to the touch but, curiously enough, the patient himself rarely complained of being chilly. The oral temperature was always subnormal but was never markedly low: it ranged from 97 to 98° F. The skin was always dry; pallor always was present. The absence of axillary and pubic hair was typical. The thinning of

\* "Basophilic degeneration" of the myocardium appears to be particularly frequent in diseases of the endocrine glands, especially of the thyroid.

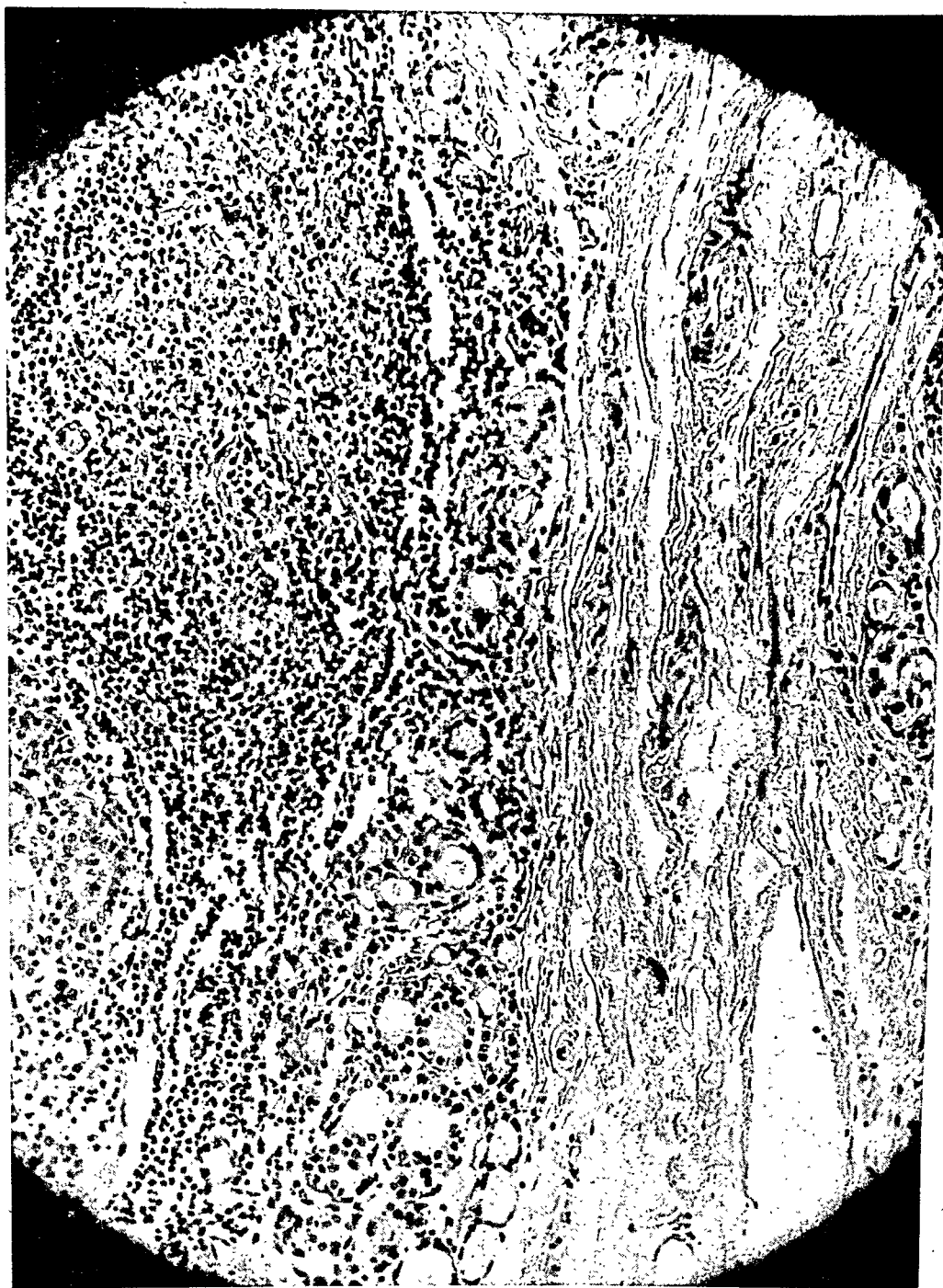


FIG. 3. Sclerosis of thyroid; large island of lymphocytes; scattered atrophic follicles.

the hair of the scalp, face, and eyebrows and the dental caries, frequently noted in the literature, were present. Genital atrophy was pronounced and apparently was more marked than that noted in most male patients suffering from this illness. Disturbances in water balance, commonly found in the condition, were evident throughout the patient's illness. Three years after symptoms appeared,

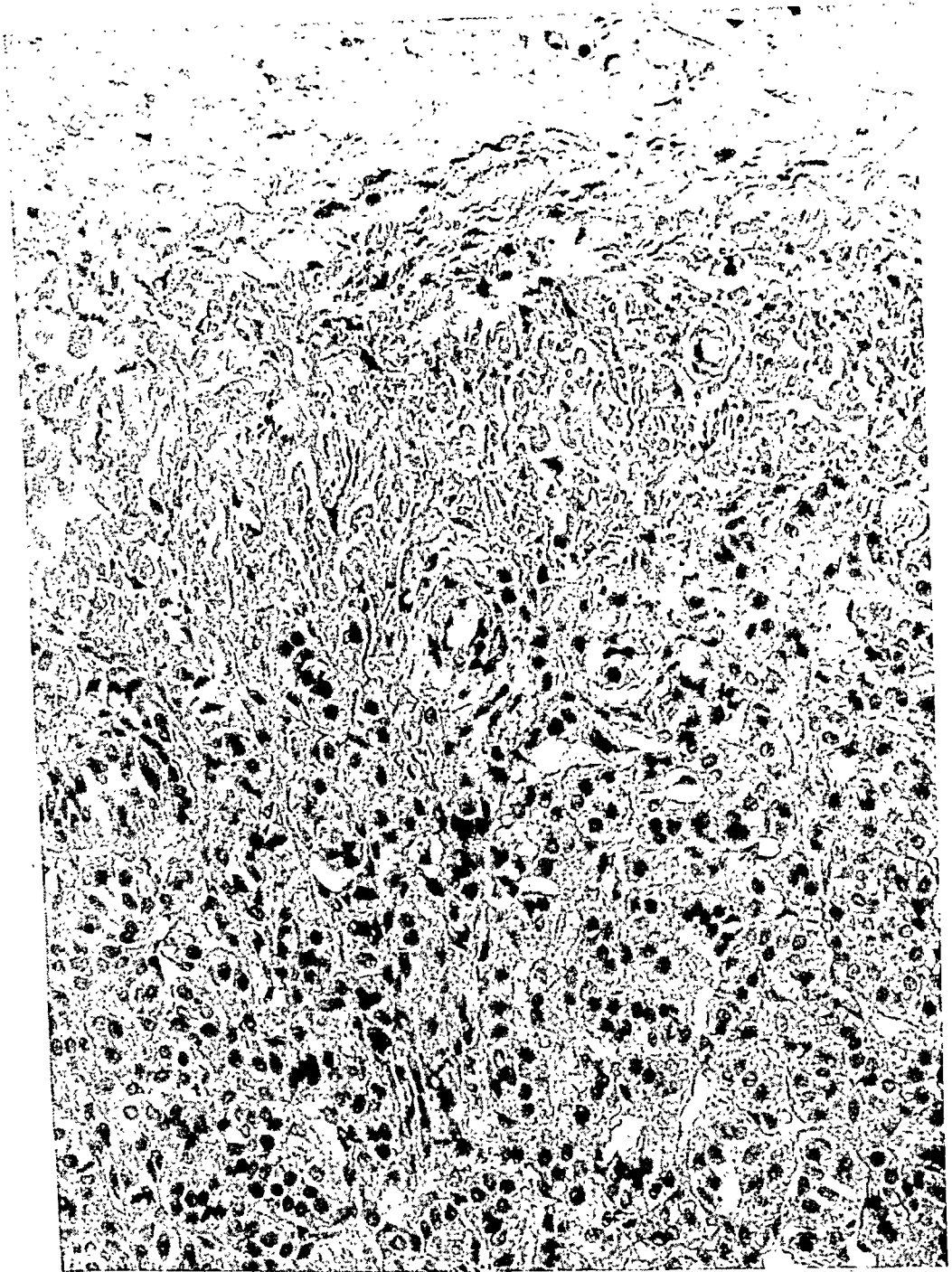


FIG. 4. Adrenal cortex with fibrosis of zona glomerulosa.

a picture like that of a diabetes insipidus was present for a few weeks. Escamilla and Lissner found such a picture to be present in 15 per cent of the group of pathologically proved cases. Edema of noncardiac origin was marked at the time of our first contact with this patient. Finally anasarca, characteristic of cardiac decompensation developed, would not respond to any type of therapy, and was

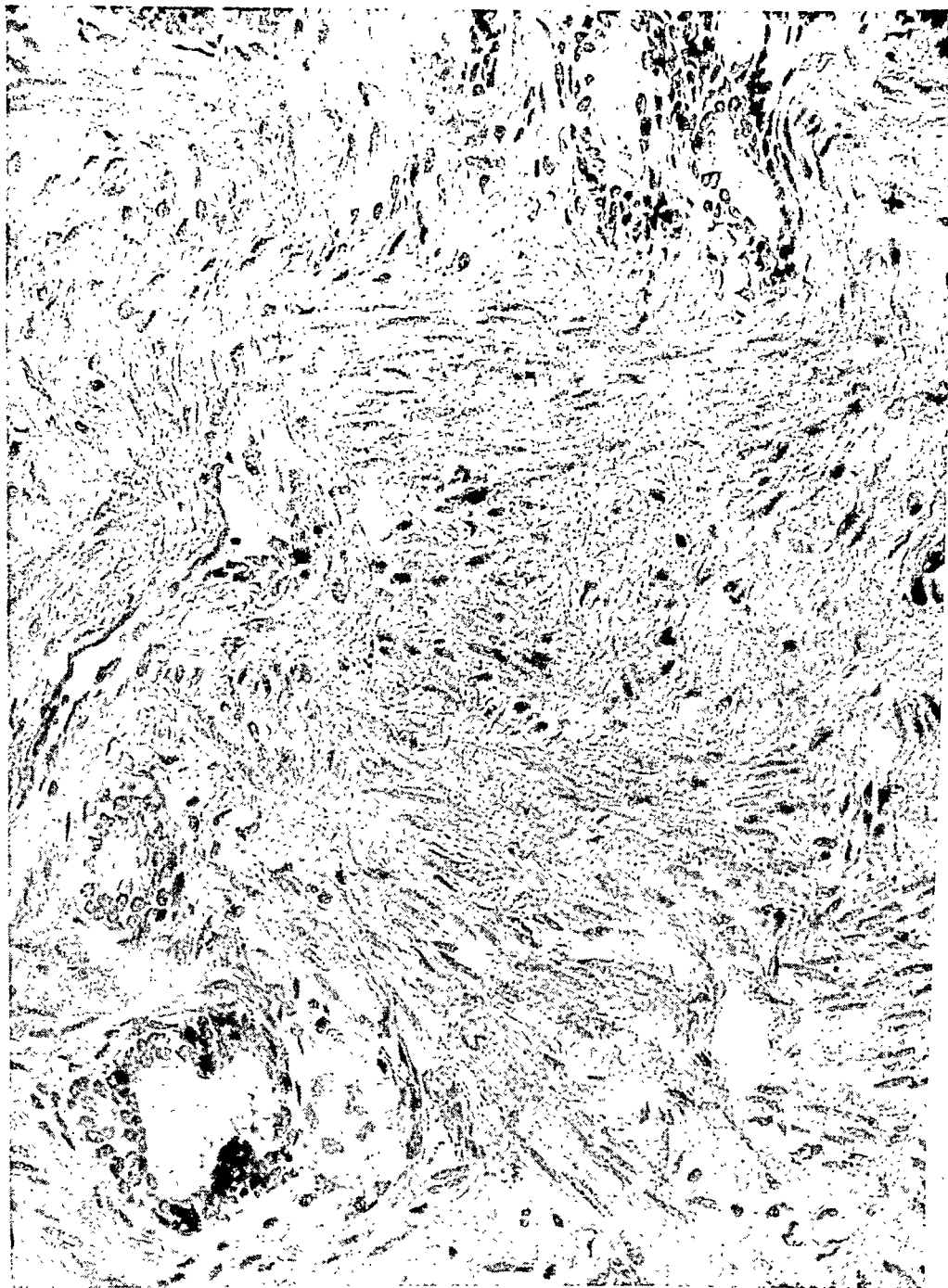


FIG. 5. Atrophy of prostate.

the ultimate cause of death. Emaciation, present in most cases, was never marked in this patient; it probably was masked to some degree by edema of one type or the other. Abnormally slow pulse rates and low blood pressures were thought by Escamilla and Lissner to be of significant frequency, but such were not displayed by our patient.



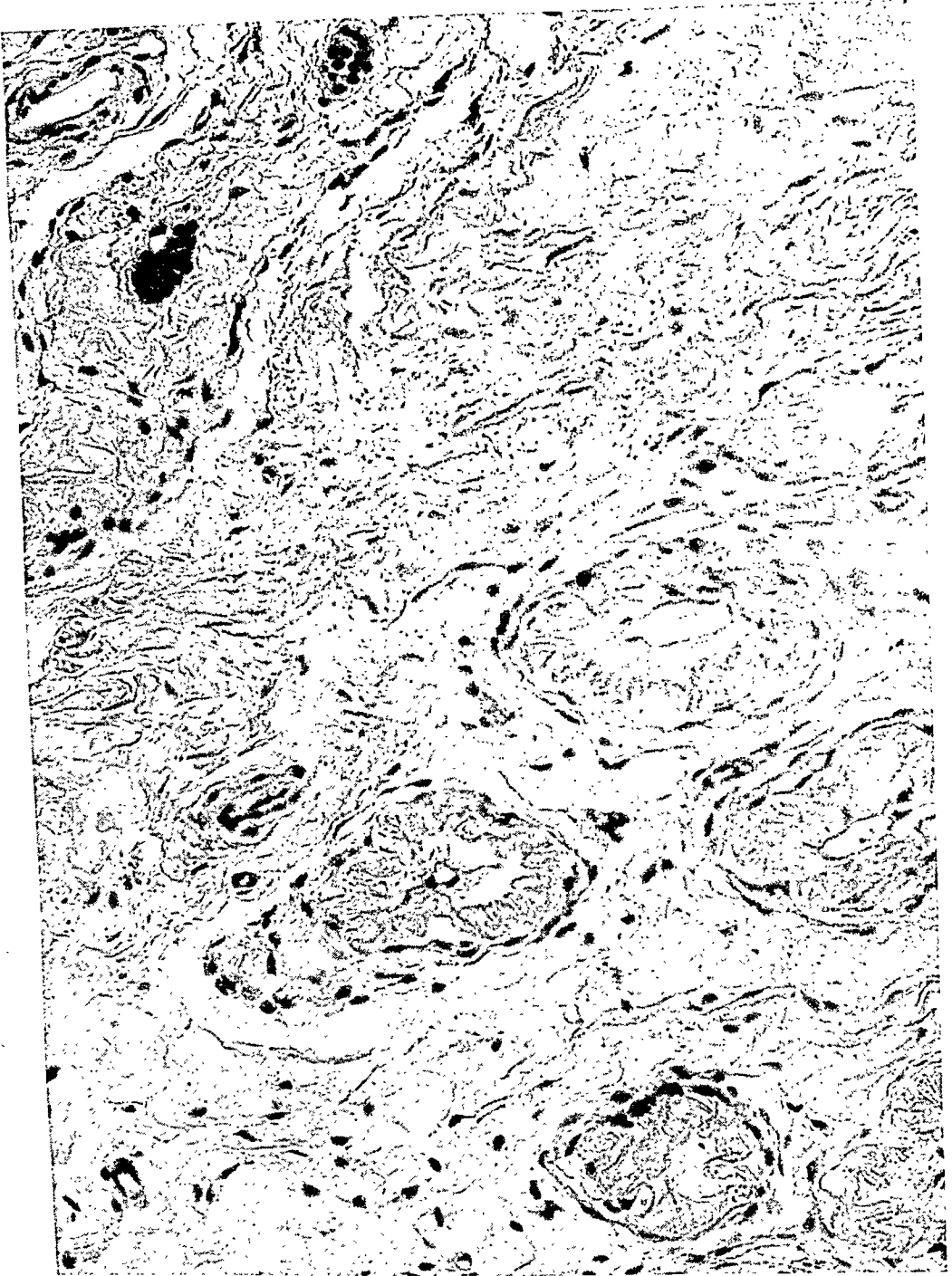


FIG. 6. Sclerosis of testis, with almost complete obliteration of tubules.

The laboratory findings in our case tended to be consistent with the findings usual in Simmonds' disease. The low basal metabolic readings have been mentioned. The fasting blood sugar levels became progressively lower as the disease progressed. The anemia was apparently of the type and degree commonly found. Escamilla and Lisser noted the frequent reporting of an increased eosinophile



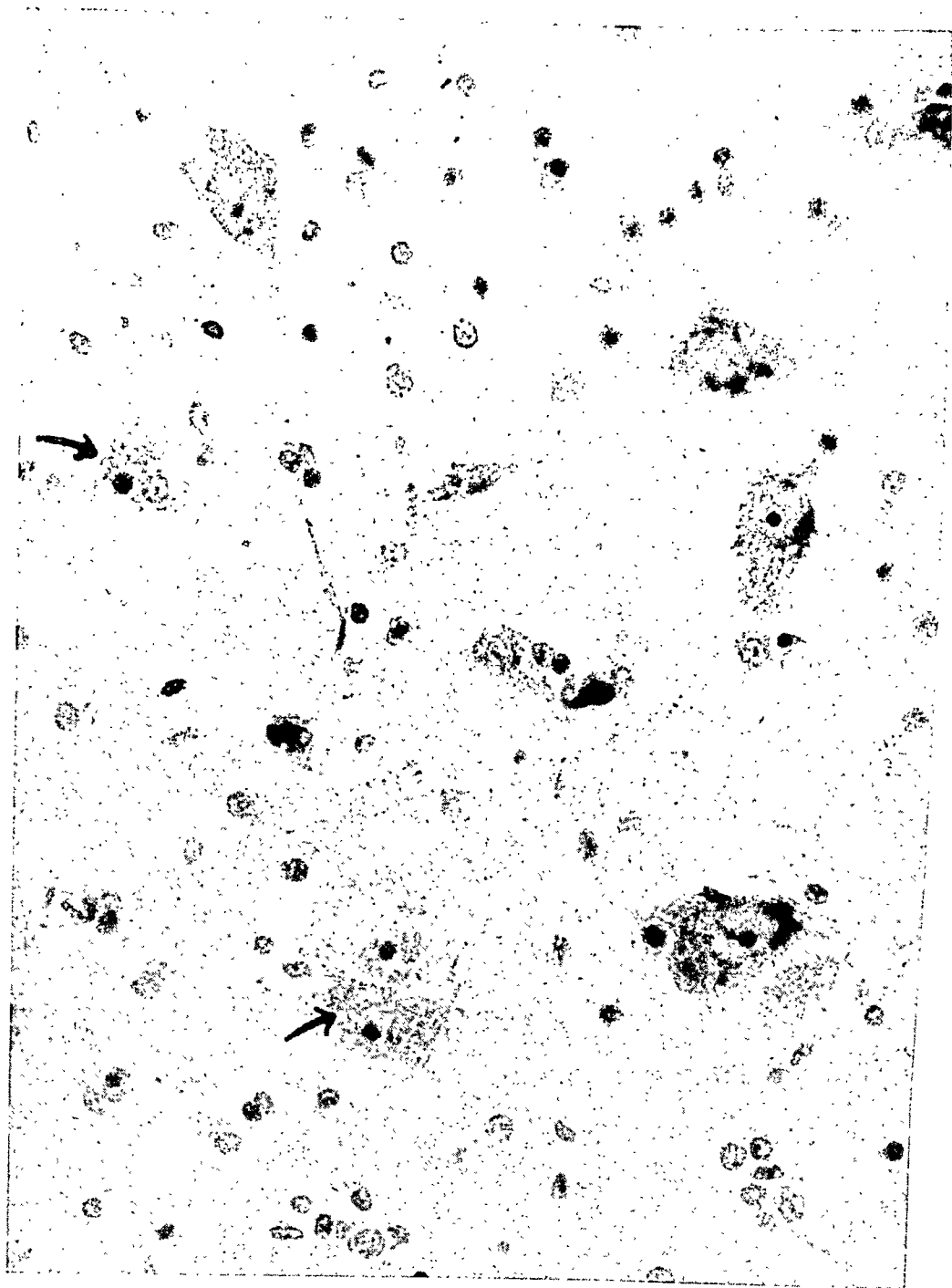


FIG. 7. Degenerating nerve cells in the nucleus supraopticus.

percentage but in our case, out of many differential blood counts, an eosinophilia of 5 per cent or more was found only twice, both times early in our observation period. The gastric acidity was within normal limits as were also the routine blood chemistry findings obtained a few months before death.

Since the 101 cases of pathologically proved Simmonds' disease all represented

fatalities; Escamilla and Lisser, in their effort to glean evidence as to the efficacy of therapy, had to deal almost exclusively with the 158 cases which were typical from the clinical standpoint. Of this group 60 per cent appeared to improve as the result of therapy. After consideration of the difficulties in the evaluation of treatment, they concluded that "however conservative or skeptical one may be, a careful reading of many of the protocols forces one to believe that in some cases specific pituitary therapy must be given credit for the extraordinary improvement which occurred."

For a period of four years our patient appeared to respond to the administration of anterior pituitary-like substance. The rapid change in the patient, particularly early in therapy, was dramatic. We do not feel that simple suggestion could have been a factor in this improvement because at the time pituitary therapy was initiated, the patient was semistuporous and did not know or care about what was being done for him. Although sustained improvement seemed so definite, it must be stated, in all fairness, that this patient's condition was never such that a diagnosis of Simmonds' disease was not apparent. We do feel, however, that as a result of the specific pituitary therapy, not only was the patient elevated to a higher plane of activity and well being but his life was prolonged by several years.

The pathologic classification of this unusual condition in a middle-aged male, without definite cachexia, is associated with the same difficulty that is encountered in many related cases, namely, the differential diagnosis between Simmonds' disease and Falt's disease (pluriglandular sclerosis). This problem has been discussed by many authors, among them Berblinger,<sup>2</sup> Meerwein,<sup>3</sup> and Castleman and Hertz.<sup>4</sup> The latter co-authors pointed out that if some "glands are sclerotic and others only atrophied, one might assume a primary lesion in one of the sclerotic glands and secondary atrophy of the others." In the case under discussion, the destruction and fibrosis of the pituitary, including the posterior lobe, were so thorough as to make it impossible to find any trace of the original tissue. Although the adrenals and prostate showed atrophy mainly, though not exclusively, the thyroid and testis exhibited sclerosis predominantly; this was, however, not quite as far advanced as that in the pituitary. One may therefore conjecture that the hypophysis was the organ primarily involved, and that its destruction caused atrophy and sclerosis of the remaining glands. Succinct histologic proof, however, cannot be given. The final outcome of this disease of 23 years' duration was a pluriglandular sclerosis, of which the primary site and ensuing course cannot be traced dependably and irrefutably. Because of the close relationship between Simmonds' and Falt's diseases, considered as possibly identical by some authors (Hirsch and Berberich<sup>5</sup>), the pathologic classification in our case appears to be of minor importance.

The etiology is questionable but three causative factors should be considered: influenza, rheumatism, and syphilis. The symptoms developed after a severe attack of influenza. In this disease inflammatory processes in the hypophysis are not uncommon (Berblinger<sup>2</sup>). However, such severe sequelae as encountered in this case are extremely rare. The rheumatic heart disease, evidenced only at autopsy, might have given rise to embolic damage of the pituitary. This assumption, however, appears remote since infarcts and their sequelae were missing in other organs and since a rheumatic etiology for Simmonds' disease has only ex-

ceptionally been demonstrated in the literature. Syphilis may play an important rôle in Simmonds' disease (Berblinger,<sup>2</sup> Jaffé,<sup>6</sup> and others). The early history of our patient points in this direction. It is apparent, however, from observation of the earlier available records and also from our own records that our patient failed to show either clinical or serological evidence of syphilis. Moreover, at necropsy, syphilitic manifestations were missing, unless the scars on the surface of the liver are considered to be of syphilitic origin, a possibility which can be neither denied nor proved. The sclerosis of the testis was in all probability a manifestation of the pluriglandular sclerosis and not one of syphilis, because the latter rarely leads to such pronounced shrinkage and homogeneous obliteration with disappearance of the interstitial cells.

The brain changes in our case were not serious and not especially characteristic. However, the scattered degenerative lesions of neurons and the glial reactions, particularly in the nuclei of the thalami and interbrain, are worth mentioning. They may have been secondary to the pluriglandular insufficiency, especially to the destruction of the posterior lobe of the pituitary. This belief was held by Gallavan and Steegmann,<sup>7</sup> who reported similar findings several years ago. The number of cases with thorough histologic examination of the central nervous system is still small. Further investigation of such cases is desirable.

#### SUMMARY

The case of a male patient, displaying the clinical and laboratory characteristics of Simmonds' disease, is presented with the following features:

- (1) a clinical course of 23 years' duration;
- (2) an apparent therapeutic response to the administration of anterior-pituitary-like substance for four years;
- (3) necropsy findings, which revealed complete obliteration of the pituitary, marked sclerosis of the thyroid and testis, and atrophy of the prostate and adrenal, together with moderate degenerative changes in the brain, particularly in the thalami and the interbrain.

#### BIBLIOGRAPHY

1. ESCAMILLA, ROBERTO F., and LISSER, H.: Simmonds' disease. A clinical study with review of the literature; differentiation of anorexia nervosa by statistical analysis of 595 cases, 101 of which were proved pathologically, *Jr. Clin. Endocrin.*, 1942, ii, 65-96.
2. BERBLINGER, W.: Die hypophysäre Kachexie (Simmonds'sche Krankheit), *Handbuch der inneren Sekretion* (M. Hirsch), 1932, C. Kabitzsch, Leipzig, vol. i, pp. 958-980.
3. MEERWEIN, F.: Ueber die multiple Blutdruesensklerose Falta, Frankfurt. *Ztschr. f. Path.*, 1938, lii, 54-79.
4. CASTLEMAN, B., and HERTZ, S.: Pituitary fibrosis with myxedema, *Arch. Path.*, 1939, xxvii, 69-79.
5. HIRSCH, S., and BERBERICH, J.: Ein Beitrag zur Frage der multiplen Blutdruesensklerose, *Klin. Wchnschr.*, 1924, iii, 483-486.
6. JAFFÉ, R.: Luetische Erkrankungen der Hypophyse, Frankfurt. *Ztschr. f. Path.*, 1922, xxvii, 324-335.
7. GALLAVAN, M., and STEEGMANN, A. T.: Simmonds' disease (anterior hypophyseal insufficiency): report of two cases with autopsy, *Arch. Int. Med.*, 1937, lix, 865-882.

## ELECTROCARDIOGRAPHIC RECORD OF A DYING HEART\*

By SOLOMON KRELL, M.D., *Bronx, New York*

## CASE REPORT

MRS. E. R., a 74 year old female, was admitted to the Hospital and Home of the Daughters of Jacob on November 21, 1940, for custodial care. The diagnosis on admission was general arteriosclerosis, coronary sclerosis, and bilateral cataracts. Her chief complaints were those of general weakness, and occasional fainting spells. Examination of the heart revealed poor heart sounds, a regular rhythm, and a blood

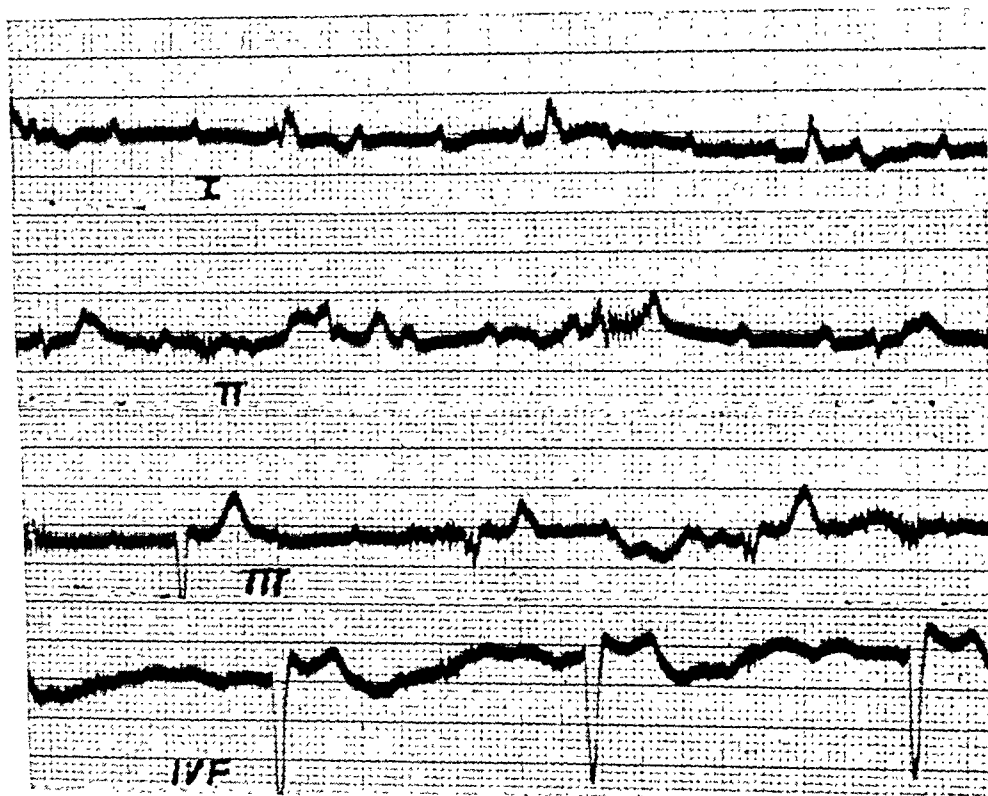


FIG. 1. Following cardiac standstill of  $1\frac{1}{4}$  minutes, 1 c.c. of epinephrine (1-1,000) intracardially. Tracing taken within a few minutes. Complete A-V dissociation but no coupling.

pressure of 180 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram taken on December 2, 1940, revealed a 2:1 A-V block, slurring and notching of the QRS complexes, a depressed ST<sub>2</sub>, inverted T<sub>2</sub> and T<sub>4</sub>, and a deep Q<sub>4</sub>.

Between January of 1940 and February of 1942, she had frequent dizzy spells and complained of occasional precordial pains and weakness. Her blood pressure ranged from 140 mm. Hg systolic and 70 mm. diastolic to 180 mm. systolic and 70 mm.

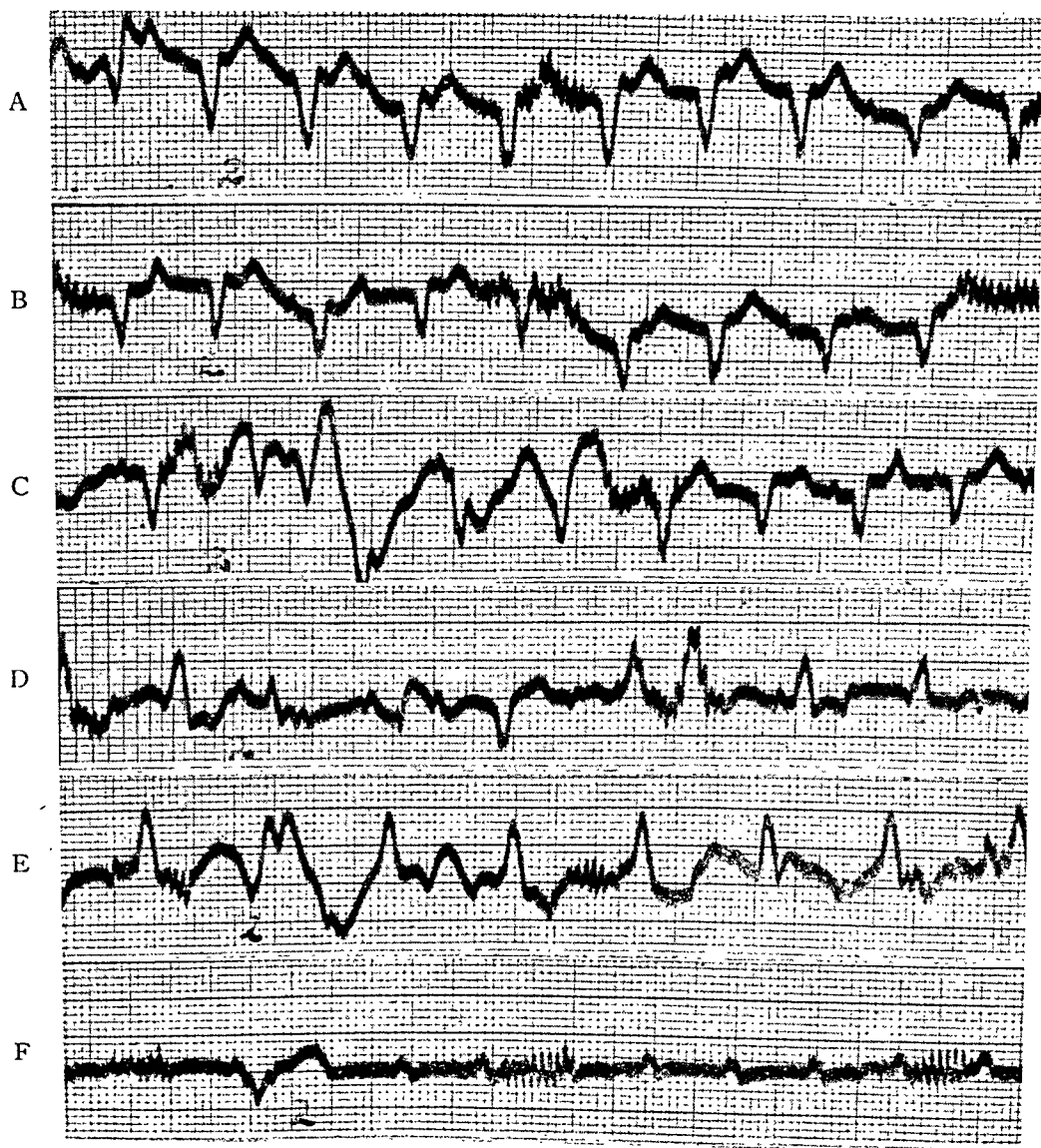
\* Received for publication January 21, 1943.

From the Hospital and Home of the Daughters of Jacob, New York, N. Y. From the service of Dr. A. A. Brill and Dr. A. S. Hyman.

diastolic. There was nothing noteworthy in the examinations of the blood and of the urine.

On February 8, 1942, she was admitted to the hospital with a temperature of 101° F., and a diagnosis of acute upper respiratory infection was made. Shortly after admission, she had a sudden sinking spell. Her pulse was rapid, and the blood pressure at that time was 170 mm. Hg systolic and 100 mm. diastolic. The following day an electrocardiogram showed complete A-V dissociation with a coupled rhythm. She was complaining of severe dizziness. There was moderate orthopnea as well as cyanosis of the lips. The lungs were clear. The heart showed considerable enlargement to the left, with the heart sounds weak; the rhythm was coupled with a total rate of 30 to 35. Neither the liver nor the spleen was palpable. She was given aminophyllin intravenously and placed on ephedrine, gr. 3/8, every three hours.

On February 17, 1942, her condition was much worse. There was marked cyanosis and restlessness, with Cheyne-Stokes respiration. Complete heart block and coupled rhythm persisted. During an examination, the patient suddenly began to



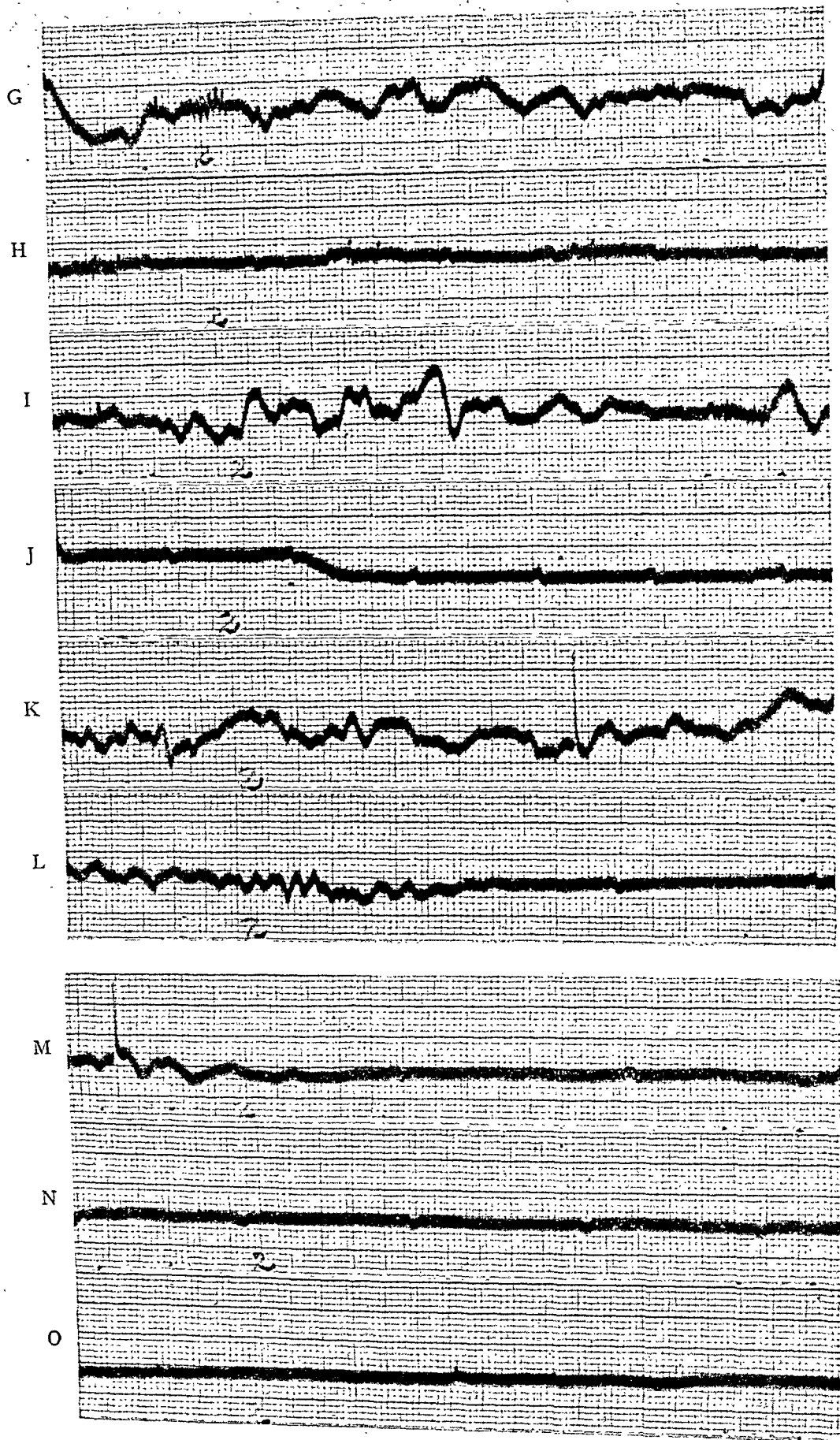


FIG. 2. Continuous strip of Lead II (A-O) following a convulsive seizure.

struggle, turned a deep purple, and both heart and respiration stopped. Following cardiac standstill of one and a quarter minutes, she was given 1 c.c. of epinephrine (1-1,000) intracardially. Cardiac activity was once more resumed, she began to breathe again, and her color was improved. An electrocardiogram taken within a few minutes showed complete A-V dissociation, but no coupling (figure 1).

Twenty-four hours later the patient had a convulsive seizure. When that subsided, a continuous strip of Lead II was taken until the time of death, which followed in about 10 minutes.

It will be noted that strips A, B, C, D, E, and F, show ventricular tachycardia with runs of ventricular fibrillation. At the end of strip E, heart sounds were no longer audible, and clinically, the patient was pronounced dead. Electrical activity continued, however, in the form of ventricular fibrillation (strips G, I, K, L), punctuated by long pauses of ventricular standstill, while the auricles continued to beat regularly (strips H and J). In strips K and M, there appears a single normal QRS complex. There is persistent auricular activity at a diminishing rate, long after all semblance of ventricular activity had ceased.

### DISCUSSION

Records of the dying heart have appeared in the literature from time to time. The first one was published by Rohmer<sup>1</sup> in 1911. Since then, numerous other observers have published electrocardiograms taken at or near death. To mention only a few, in 1923 Schellong<sup>2</sup> reported 20 cases; the following year Kahn and Goldstein<sup>3</sup> reported their observations on the dying heart; Willius<sup>4</sup> wrote in 1930, Jezer, Master and Schwartz<sup>5</sup> in 1936, and Formigne<sup>6</sup> in 1938. All of these records show abnormalities of rhythm and QRS complexes. The rhythm abnormalities run from complete A-V dissociation through ventricular tachycardia to ventricular fibrillation and standstill. Some cases have been reported where ventricular activity ceased before that of the auricles, and in others, the sequence was reversed. In the case reported upon here, the auricles showed electrical activity for at least 10 minutes after ventricular standstill.

Jezer, Master, and Schwartz<sup>5</sup> stressed the danger of epinephrine in cases of complete A-V dissociation, explaining that this drug has a tendency to initiate ventricular tachycardia. Our patient lived for 24 hours following intracardial injection of 1 c.c. of 1-1,000 epinephrine. During these 24 hours the rhythm was that of complete heart block, but, curiously, the coupling which had been previously observed disappeared. We doubt whether the terminal ventricular tachycardia and fibrillation were in any way related to the epinephrine which had been administered 24 hours previously. Obviously, in this case, as in others elsewhere reported, some irritable focus or foci were established, which took precedence over the previously functioning idioventricular rhythm. Thus, ventricular tachycardia and fibrillation were initiated, terminating in cardiac standstill.

### SUMMARY

An electrocardiographic record is presented of a 74 year old female who had suffered some two years before death from arteriosclerotic heart disease and complete A-V dissociation. In the course of an acute upper respiratory infection, she developed cardiac standstill for one and one-quarter minutes. Cardiac activity was resumed following an intracardiac injection of epinephrine. Twenty-

four hours later, she developed ventricular tachycardia, ventricular fibrillation, and cardiac standstill.

I wish to acknowledge with thanks the aid extended to me by Bernard Newman, B.S., Ch.E., in charge of the pathology laboratories at the Hospital and Home of the Daughters of Jacob.

#### BIBLIOGRAPHY

1. ROHMER: München med. Wchnschr., 1911, lviii, 2358. (Reference of KAHN and GOLDSTEIN.<sup>3</sup>)
2. SCHELLONG, F.: Electrocardiography of heart in death, Klin. Wchnschr., 1923, ii, 1394-1399.
3. KAHN, M. H., and GOLDSTEIN, I.: The human dying heart, Am. Jr. Med. Sci., 1924, clxviii, 388.
4. WILLIUS, F. A.: Clinical electrocardiograms, their interpretation and significance, 1929, W. B. Saunders, Philadelphia.
5. JEZER, A., MASTER, A. M., and SCHWARTZ, S. P.: Observations on the mechanism of the dying heart in patients with Adams Stokes syndrome due to standstill of the ventricles, Am. Heart Jr., 1936, ii, 303.
6. FORMIGNE, P.: Apnea and convulsions following standstill of the heart, Am. Heart Jr., 1938, xiii, 129.

### WOLFF-PARKINSON-WHITE SYNDROME SIMULATING MYOCARDIAL INFARCTION \*

By HERBERT EICHERT, Lieut. (M.C.), U.S.N.R., *Boston, Massachusetts*

THE purpose of this paper is to report a case of the so-called Wolff-Parkinson-White syndrome, a relatively benign cardiac abnormality, which simulated and was misinterpreted as myocardial infarction.

Characteristic electrocardiograms appeared in the literature many years ago,<sup>1, 2</sup> but their significance and the various features of the syndrome were first clearly defined by Wolff, Parkinson, and White in 1930,<sup>3</sup> and the relative benignity of the condition established. Numerous subsequent publications<sup>4, 5</sup> have appeared in journals of limited circulation and consequently the knowledge of this syndrome has not been widely disseminated.

#### CASE REPORT

R. W., a salesman, was 40 years old at the onset of his illness in 1932. During this illness he resided in several different cities and the material here presented is an aggregate of the observations of various physicians who attended him, in addition to the studies of the author during the latter part of this period.

He was in good health up to the onset of the present illness. During his youth, he indulged freely in athletics and never had any symptoms which prompted him to restrict physical activity. During adult life he worked actively at his occupation, and was never aware of any undue shortness of breath or heart consciousness.

In the spring of 1932, during a period of emotional strain, and after an unusually heavy session of handball, he "wilted" and was seized with an intense pain in his

\* Received for publication February 9, 1944.



chest accompanied by dyspnea. He went home and to bed but did not feel it necessary to call a physician. Although the symptoms gradually subsided, he was unable to sleep until 10 hours later, when the pain disappeared. The following day, he felt washed out and under par, but was able to carry out the usual duties of his occupation.

After several days of continued "ill health," he decided to seek medical attention and was studied in the Out-Patient Department of a large hospital. The general physical examination is said to have been negative at the time, but the electro-

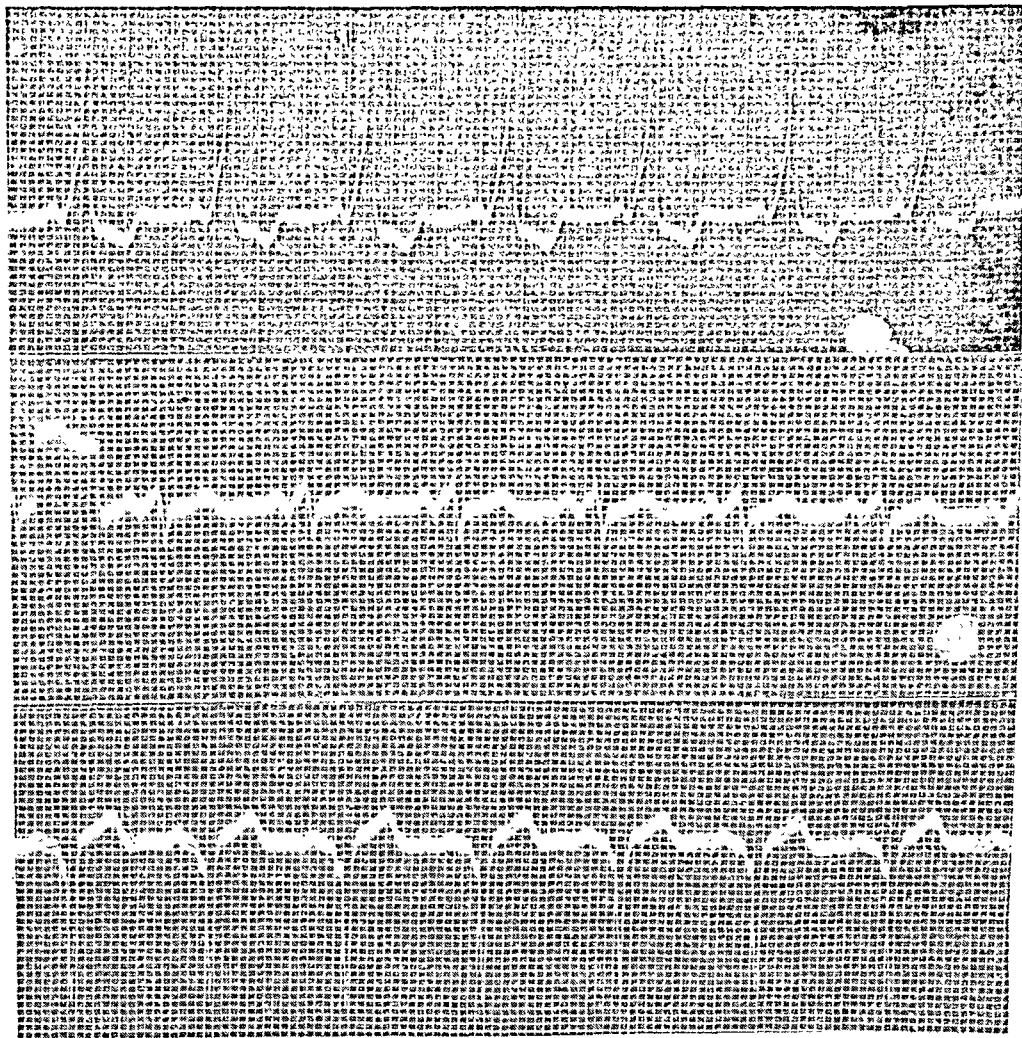


FIG. 1. Typical initial electrocardiogram on patient demonstrating the important features of the Wolff-Parkinson-White type of tracing. Viz: P-R interval of 0.1 sec. or less, slurring and widening of the QRS with T waves opposite main ventricular deflection.

cardiogram was abnormal. This electrocardiogram is now unobtainable, but the description suggests that it is identical with subsequent tracings. Such a typical tracing is reproduced in figure 1. These bizarre findings were interpreted as indicating coronary insufficiency with atypical bundle branch block.

The patient was cautioned against physical overexertion, but was permitted to return to his work. He continued to have transient episodes of breathlessness, precordial distress and palpitation, and these symptoms became worse during the ensuing

year. Nervousness and apprehension became a problem of growing concern until finally he spent most of the day in bed in an effort to alleviate his symptoms. For almost a year he remained practically bedridden. Available fragmentary medical records covering this period indicated that his physical status remained essentially unchanged and the electrocardiographic tracings continued to be identical with those previously recorded.

Two years after the initial "attack" he began to improve. He was able to go on short vacation trips and moved to another city. A physical examination at that time showed a well-nourished, well-preserved man in no apparent pain or respiratory distress. Blood pressure was 120 mm. Hg systolic and 78 mm. diastolic, and the pulse rate 82 per minute. The heart was not enlarged by percussion and the heart sounds were normal. There was no physical evidence of cardiac insufficiency. A tele-roentgenogram showed a heart shadow with a suggestion of enlargement of the left ventricle, the cardiothoracic ratio being 14/24. This, however, was explainable by his physical stature. An electrocardiogram was identical with that previously recorded.

In 1938, he became extremely nervous, lost weight and the pulse rate was said to average 100 per minute. No basal metabolic rate determination or electrocardiogram was done at the time but he took Lugol's solution for two months and improved greatly. Subsequent examination revealed no evidence of hyperthyroidism and no enlargement of the thyroid. There had been no recurrence of a similar condition.

Six months later, a routine electrocardiogram was unlike any of those previously obtained (figure 2). The P-R interval and QRS duration were now normal; small Q waves were present in Leads II and III, and  $T_2$  and  $T_3$  were inverted. Electrocardiograms taken during the following year were of variable patterns. Some with normal P-R interval had only a  $Q_3$  with upright  $T_2$  and  $T_3$  (figure 3). At other times, complexes with both short P-R interval and normal P-R interval were found in the same tracing. At that time, no satisfactory explanation was apparent for these reversions from one to the other type of rhythm, which were spontaneous, but could not be induced by medication or carotid sinus stimulation.

The patient's general health continued to be good up to the time of our examination. There had been no changes in his physical examination and no signs of cardiac failure.

#### COMMENT

The manifestations in this case, on which the diagnosis of myocardial infarction were based, included a history of severe and protracted subpectoral pain and an electrocardiogram interpreted as showing bundle branch block. In 1940 the correctness of the original diagnosis was questioned. Continued observations over an eight year period did not confirm the serious implications of myocardial infarction and bundle branch block. Careful revaluation of all the evidence led to the belated conclusion that all the findings could be adequately explained by the Wolff-Parkinson-White syndrome in a patient with neurocirculatory asthenia on the following basis.

The patient with Wolff-Parkinson-White syndrome is prone to disturbances of cardiac rhythm, palpitation and cardiac awareness. These changes in rhythm may occur after exercise, due to paroxysmal tachycardia or numerous ectopic impulses. Such disturbances in rhythm may be accompanied by a sensation of precordial oppression, which may approximate a severe pain and a sensation of dyspnea in sensitive individuals.

This patient had a severe attack of precordial pain after a strenuous session of handball, but weakness and "wilting" were the outstanding symptoms. Palpi-

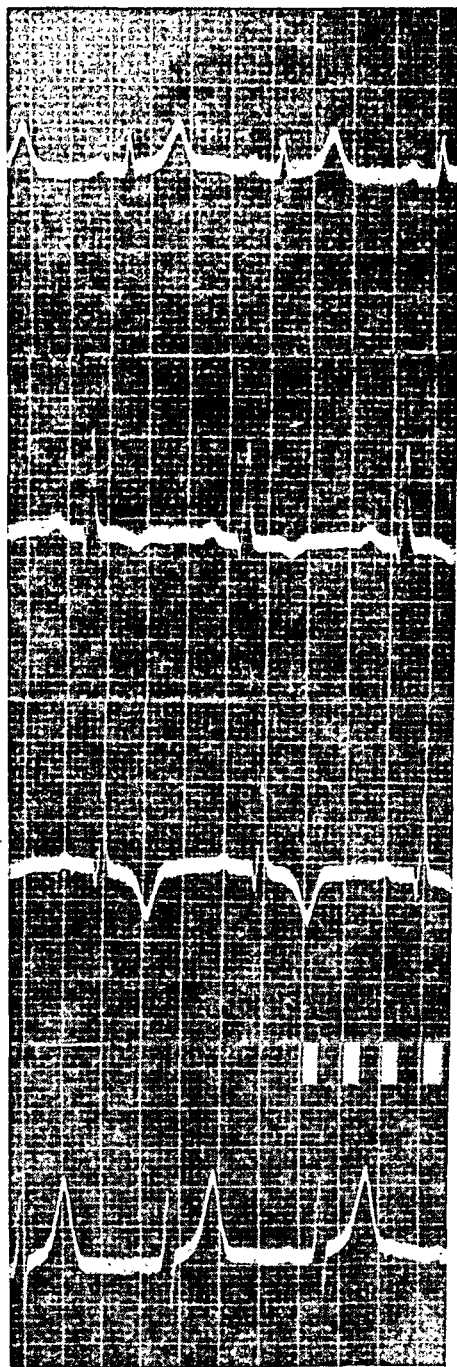


FIG. 2. Electrocardiogram, November, 1939, showing reversion to normal rhythm with P-R interval of .18 sec. and QRS duration of .08 sec. Note  $Q_2$  and  $Q_3$  and inverted  $T_2$  and  $T_3$ , the changes which suggested posterior myocardial infarction.

tation was a prominent complaint and may have been due to paroxysmal rapid heart action.

Subsequent study failed to reveal evidence of organic heart disease, and re-evaluation of the clinical picture is consistent with neurocirculatory asthenia in a

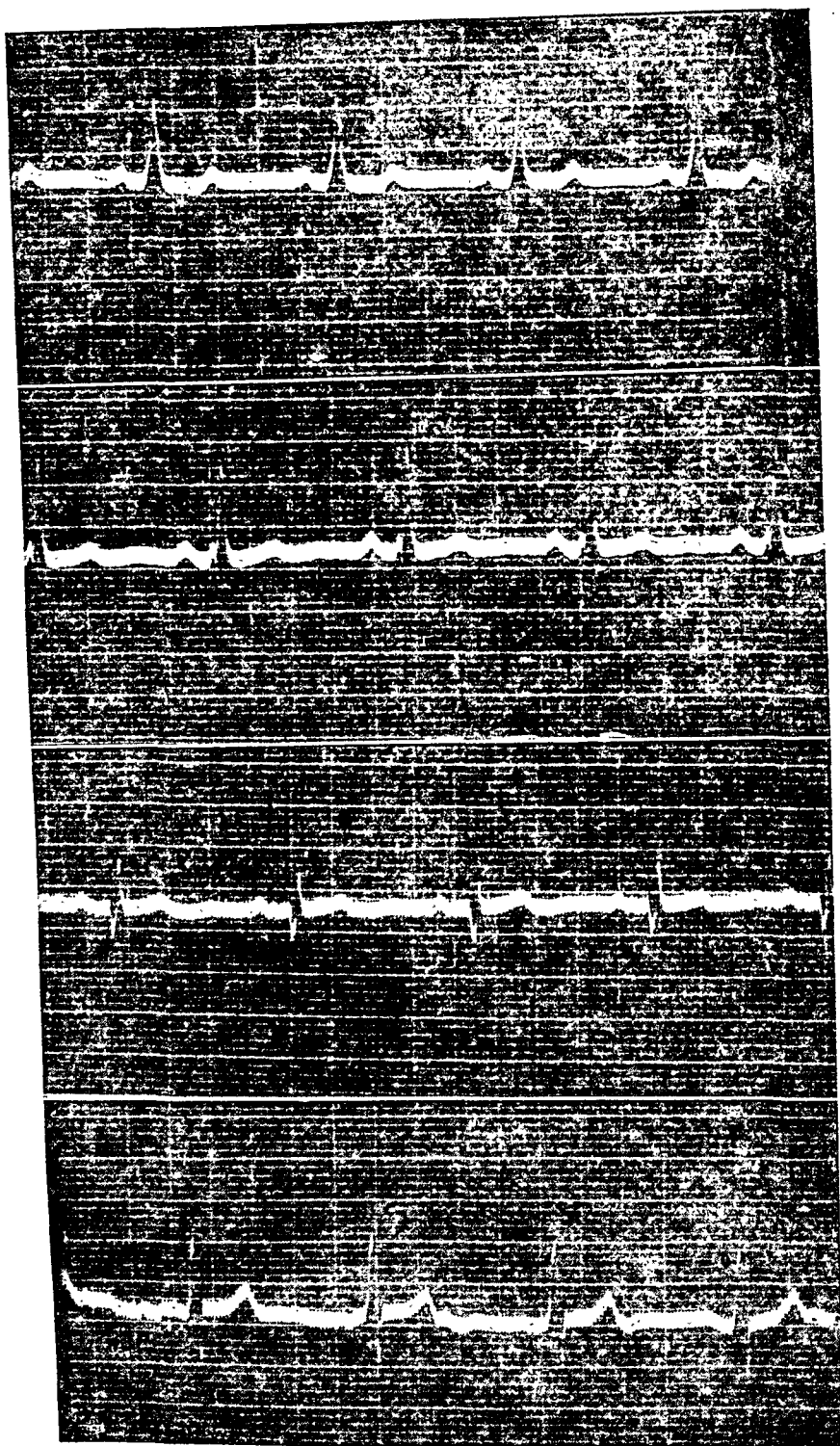


FIG. 3. Tracing showing normal rhythm. Note change in  $Q_2$  and  $Q_3$  and  $T_2$  and  $T_3$  compared to figure 2.

patient with the Wolff-Parkinson-White syndrome. Reassurance resulted in a significant amelioration of his symptoms.

It is known that the electrocardiograms of the Wolff-Parkinson-White syndrome may revert to a normal type spontaneously or in response to extracardiac stimuli or medication. In 1938 for the first time a tracing showed a normal P-R interval and normal QRS duration, but with a downward  $Q_2$ ,  $T_2$ ;  $Q_3$ ,  $T_3$  pattern. This suggested posterior myocardial infarction, which could however be excluded because these findings were inconstant (figure 3); furthermore, such unexplainable alterations in the electrocardiogram may occur in the Wolff-Parkinson-White syndrome.

### SUMMARY

1. A case is presented in which a diagnosis of myocardial infarction was made on a patient having a history of precordial pain and an abnormal electrocardiogram suggesting bundle branch block.

2. Later studies of this patient led to the conclusion that all of his symptoms and abnormal electrocardiographic changes were explained on the basis of the relatively benign Wolff-Parkinson-White syndrome in a patient with neuro-circulatory asthenia.

3. It is important that all physicians interpreting electrocardiograms should be thoroughly familiar with the Wolff-Parkinson-White syndrome in order to avoid the error made in the case herein reported.

The author wishes to express his gratitude to Dr. Louis Wolff of the Beth Israel Hospital, Boston, Massachusetts, for his generous guidance in the preparation of this report.

### BIBLIOGRAPHY

1. WILSON, F. N.: A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram, *Arch. Int. Med.*, 1915, xvi, 1008.
2. WEDD, A. M.: Paroxysmal tachycardia, *Arch. Int. Med.*, 1921, xxvii, 571.
3. WOLFF, L., PARKINSON, J., and WHITE, P. D.: Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia, *Am. Heart Jr.*, 1930, v, 685.
4. BUTTERWORTH, J. SCOTT, and POINDEXTER, CHARLES A.: Short P-R interval associated with prolonged QRS complex, *Arch. Int. Med.*, 1942, lxix, 437.
5. CLAGGETT, A. HENRY: Short P-R interval with prolonged QRS, *Am. Heart Jr.*, 1943, xxvi, 55.

## EDITORIAL

### *RATIONAL USE OF THE VITAMINS*

WHEN, if, and how to take vitamins, what vitamins to take, whether to take pure vitamins or crude vitamin-complexes—these are only some of the questions that today must perplex the layman and indeed the physician as well, since the latter is called upon constantly to prescribe vitamins, interpret their effects, and above all to “debunk” vitamins. If we were to accept some of the more flowery claims for the vitamins that are glibly passed out to us over the radio, we might wonder how the human race ever managed to survive to see the dawn of the twentieth century with the advent of vitamins for all. And we should perhaps be astounded to learn that the great majority of human beings got along nobly in the olden days, even though they were not supplied with their daily vitamin requirement compactly assembled in a colorful little capsule. To put it mildly, the advertising claims for vitamins have been grossly exaggerated.

What then are vitamins and when are they indicated? Vitamins are not food nor even substitutes for food; they are not cure-alls nor do they provide energy, calories, or body-building materials. Vitamins may be defined as essential accessory food factors which act as catalytic agents aiding in the assimilation and utilization of foods in the body and playing all-important rôles in the metabolic processes of the body and the maintenance of various body tissues in a normal healthy condition. The body is incapable of synthesizing the majority of the vitamins (vitamin D being a notable exception), so that we must rely upon extrinsic sources of supply in the foods that we eat. Fortunately, the vitamins of proved importance in human nutrition are for the most part widely distributed in nature; hence, a well-balanced diet including meat, eggs, butter, milk, green and yellow vegetables, fresh fruits, and whole grain cereals should easily supply the daily vitamin requirement for the average healthy individual. Since no amount of vitamins is helpful without the essential foods, it is easy to understand why nutrition experts place the greatest stress on diet, emphasizing the need for eating the right foods in the right quantity. Experts declare that the average person who has been on a properly balanced diet has no business taking vitamin concentrates. The fact that the vitamins are non-toxic in the usual recommended doses is not sufficient justification for their indiscriminate use by healthy persons, even though this freedom of the vitamins from toxic side-effects is perhaps most fortunate in view of the ruthless manner in which commercial preparations are being foisted upon a gullible public.

At the present time seven vitamins, the chemical structures of which have been definitely established, are of proved importance in human nutrition, namely: (1) vitamin A or its precursor carotene, (2) vitamin B<sub>1</sub> (thiamin chloride), (3) vitamin B<sub>2</sub> (riboflavin), (4) nicotinic acid, (5) vitamin C

(ascorbic acid), (6) vitamin D (irradiated ergosterol), and (7) vitamin K (a naphthoquinone). In addition there is highly suggestive evidence that certain other recently identified vitamins of proved importance to lower animals are probably necessary for human nutrition as well. Among the latter are vitamin B<sub>6</sub> (pyridoxin), pantothenic acid, biotin, choline, and vitamin E (alpha tocopherol). It must be stressed that the actual function of these vitamins in human nutrition and the minimal human requirement are completely unknown. Nevertheless, small quantities of these chemicals have already been incorporated into a number of the current polyvitamin capsules in purely arbitrary dosage. On the other hand, there are undoubtedly a number of as yet unidentified vitamins important to human beings that can only be obtained by ingestion of the original food sources. This unknown factor furnishes one of the most potent arguments in favor of relying upon a well-balanced diet rather than commercial vitamin capsules for our daily vitamin intake.

When we encounter the full-blown clinical picture of beri-beri, pellagra, or scurvy, we do not hesitate to prescribe thiamin, nicotinic acid, or ascorbic acid respectively in massive doses with full knowledge that there is a deficiency of a specific known vitamin in each instance and that the administration of the missing factor will promptly alleviate the presenting symptoms. Equally well established are the indications for vitamin D in rickets and osteomalacia (with or without tetany), vitamin A in xerophthalmia and night-blindness, riboflavin in cheilosis and corneal vascularization, and vitamin K in the hemorrhagic diathesis associated with obstructive jaundice. In all instances, however, it is important to remember that, although the clinical manifestations may point largely to the deficiency of a single vitamin, a multiple deficiency frequently exists and the patient should be treated accordingly with a well balanced diet supplemented by the particular vitamin which is obviously lacking.

Far more difficult to recognize than the classical deficiency syndromes just mentioned are the vastly more numerous instances of subclinical deficiency, such as for example the pre-scorbutic or pre-pellagrous state. In this connection, the importance of an accurate dietary history cannot be too strongly emphasized, for it is only with the aid of such a history that the subclinical deficiency will be suspected. Conclusive proof of subclinical deficiency may then be obtained in certain cases by applying the various clinical methods of vitamin assay that have been worked out and by performing therapeutic tests. For example, let us consider subclinical thiamin deficiency. Anorexia, nausea, and nervous irritability have been shown to be early symptoms of thiamin deprivation, yet it would be pure folly—commercial advertisers notwithstanding—to conclude that all victims of these commonplace symptoms are suffering from thiamin deficiency or “B-complex deficiency.” As a matter of fact, a good dietary history supplemented with urinary thiamin determinations would undoubtedly rule out a deficiency basis

in the great majority of patients with these complaints, and there would be no point in plying this majority with thiamin or other vitamins. On the other hand, the *temporary* administration of synthetic vitamins and crude vitamin complexes would seem to be justified in the treatment of individuals whose dietary habits had been so poor as to justify the suspicion of subclinical vitamin deficiency. The ultimate goal, of course, in treating such patients would be to educate them to the selection of a balanced diet in order that they might eventually discontinue the prescribed vitamin supplements.

So far we have shown little enthusiasm for vitamin therapy except in the relatively rare instances of outspoken deficiency. However, there are a number of conditions under which vitamin deficiency, either clinical or more often subclinical, is likely to develop. In many of these conditions, it may be impossible, impractical, or imprudent to treat the patient by adequate dietary measures alone; under these circumstances a real indication for supplements of synthetic vitamins and crude vitamin-complexes arises.

These abnormal conditions may be grouped under several broad headings:

- (1) *Decreased Intake of Vitamins* such as may occur in alcoholics who forget to eat, victims of gastrointestinal disorders such as ulcer or spastic colon where the patient may be afraid to eat because of pain, the edentulous and other patients on restricted diets (e.g. Sippy diet, reducing diets, elimination diets), post-operative patients, and febrile or psychiatric patients with anorexia.
  - (2) *Impairment of Absorption* such as may occur in gastrointestinal disorders characterized by vomiting or diarrhea (e.g. pyloric obstruction, ulcerative colitis, fistulas), sprue with defective absorptive surface, reduction of absorptive surface (short-circuiting operations and intestinal resections), achlorhydria, obstructive jaundice (fat-soluble vitamins not well absorbed in the absence of bile salts), and excessive intestinal putrefaction.
  - (3) *Increased Excretion* as in polyuria, diuresis, diarrhea, and lactation.
  - (4) *Increased Requirement* as occurs in pregnancy and lactation, prolonged fevers, hyperthyroidism, diabetes (?), marked overactivity (e.g. manic psychosis or delirium), and excessively high carbohydrate diets.
  - (5) *Impaired Utilization* as for example in hepatic disease and diabetes mellitus (?).
- Frequently a coexistence of two or more of the five conditions will be encountered in a single patient.

Granting that definite though limited indications for therapy with pure vitamins and vitamin complexes exist, we must next decide what constitutes a well balanced polyvitamin capsule. Such a capsule should contain at least the minimum normal daily adult requirement (as far as is known) of vitamins A, C, D, thiamin, riboflavin, and nicotinic acid: that is, vitamin A 4,000 U.S.P. units, vitamin D 400 U.S.P. units, thiamin hydrochloride 1 to 2 mg., riboflavin 2 mg., nicotinic acid (or the amide) 10 to 20 mg., ascorbic acid 30 to 50 mg. There is no need for the inclusion of vitamin K in such a capsule since the therapeutic indications for this vitamin are very specific and relatively rare. Furthermore, the addition of certain of the more recently



identified B-vitamins such as pyridoxine, pantothenic acid, and choline to such a capsule has little justification at the present while we are still completely in the dark as to the human requirement for these substances. When prescribing polyvitamin capsules, it is desirable to recommend a well balanced capsule such as has been described above. As a result of sales competition in an attempt to keep the price down, a number of very inferior capsules have been placed on the market. By skimping on certain of the more expensive ingredients, a firm can manufacture a relatively cheap capsule which may readily appeal to an unsuspecting public. The writer has found it expedient to note the riboflavin content of the various vitamin capsules in evaluating their relative merit; it is obvious that a capsule which contains "200 gammas" (200 micrograms or 0.2 milligram) of riboflavin is far inferior to one containing 2.0 milligrams of riboflavin, even though to the lay purchaser the figure "200" may appear the more impressive. In situations where supplementary vitamins are definitely indicated, it is well to prescribe in addition to a balanced capsule of pure vitamins some crude B-complex preparation such as yeast powder or crude extracts or concentrates of yeast, liver, or rice polishings in order to furnish the patient with important vitamins as yet unidentified. Vitamin-fortified white breads and cereals, though superior to the unfortified, are less nutritious than whole-grain breads and cereals.

On the basis of this discussion, we may now attempt to answer the questions posed in the opening paragraph. To the layman, we can say: if you are healthy, you should make a point of eating a well balanced diet and you will have no need for extra vitamins; if you are in ill health or obliged to follow a restricted diet for some special reason, choose your doctor rather than the radio for your guide as to what vitamin preparation you should take. And to the physician: educate your patients whenever possible to a well balanced diet and advise this group to forget about supplementary vitamins; in cases when additional vitamins are indicated, prescribe a well balanced polyvitamin capsule supplemented with some crude source of the B-complex; and by all means continue to "debunk" the vitamins to the world at large.

W. H. B.

## REVIEWS

*The Principles and Practice of Cardiology.* By CRIGHTON BRAMWELL and JOHN T. KING. 509 pages; 25.5 × 16.5 cm. Oxford University Press, London. 1942.

This textbook follows a somewhat unusual plan for a book written on the subject of heart disease, in that it is divided into two parts, labelled "General Cardiology" and "Special Cardiology." Such a division is commonly seen in textbooks on pathology, but in this case the two parts are written by different authors.

The first section by the English author contains a number of rather surprising statements. In a discussion of heart failure the following statement is made about the association of auricular fibrillation with heart failure: "So frequent is this association that it is indeed difficult to collect a large series of congestive heart failure with normal rhythm."

In the section on treatment one finds the following: "Leeches, once so popular, are undoubtedly rarely used for therapeutic purposes. Nevertheless I have repeatedly obtained striking relief of pain due to hepatic congestion by the application of three or four leeches over the engorged liver." The use of cantharides is recommended in the treatment of acute pericarditis as a counter-irritant. The following statement is worth quoting in its entirety: "The ideal method of administering oxygen is to place the patient in an oxygen chamber. Unfortunately the cost of erecting such a chamber rules out this method except for research purposes. A modification of the oxygen chamber, namely, the oxygen tent as devised by the late Dr. E. P. Poulton, overcomes the financial embargo. I personally have used such a tent on two or three occasions with satisfactory results, but the difficulty of nursing the patient in the tent has prevented that method from gaining general popularity."

In the same section of "General Cardiology" the important subject of heart sounds is presented in confused fashion. Not only is the authors' terminology misleading, but he has completely overlooked the important contributions to the field made by North and South American investigators in the field of phonocardiography.

The section on "Special Cardiology" is somewhat better, but the important subject of rheumatic heart disease is presented in sketchy fashion, and the broader aspects of rheumatic fever as a long-term systemic disease are not included.

The limitations of space do not permit a cataloguing of even the most obvious deficiencies of this book. It adds nothing to the volume of literature which has already accumulated on the subject of heart disease. The text contains too many references to specific cases for a formal work on heart disease. This method of teaching is permissible in the clinic but is a serious drawback to an orderly presentation of the subject of heart disease.

C. W.

*Synopsis of Diseases of the Heart and Arteries.* Third Edition. By GEORGE R. HERRMANN, M.S., M.D., Ph.D., F.A.C.P., Professor of Medicine, University of Texas, Galveston. Third edition. 516 pages; 20 × 13 cm. C. V. Mosby Company, St. Louis. 1944. Price, \$5.00.

A great deal of information has been crowded into the third edition of this volume. The material is divided into thirty-one chapters, of which a number might have been combined, to advantage, under more inclusive headings. The style is verbose and repetition is frequent. Many of the illustrations, particularly those picturing instruments and anatomical specimens, could have been omitted without loss. Some of the sketches are difficult to decipher because of much fine print and long legends.

The clinical descriptions are adequate and the therapeutic suggestions, for the most part, are sound. There is a tendency to list many forms of treatment, rather than to recommend one, or a few, of proved effectiveness in the hands of the author. Almost all of the electrocardiograms appear in the chapter devoted to the arrhythmias. Three figures depict the changes observed after cardiac infarction; none are shown in the sections on anginal heart failure (a poor term!), pericarditis or hypertension. Yet in the appendix are given new electrocardiographic data derived from the use of unipolar central terminal precordial leads.

In the chapter on military medicine the Schneider and 2-step tests for circulatory insufficiency, both of doubtful value, are unduly stressed. There is no bibliography but a number of articles are cited in the text. A few important references at the end of each chapter would be helpful to the serious reader.

Peripheral vascular diseases are covered in 40 pages. The author is clearly more interested and experienced in dealing with disorders of the heart. It hardly seems necessary to include formulas for the preparation of various solutions, such as physiological saline, Ringer's and isotonic glucose.

In the opinion of the reviewer, "synopses" such as this have no place in medical literature. The approach to knowledge cannot be both comprehensive and short. The busy practitioner or the student will find excellent, concise accounts of cardiovascular diseases in some of the standard text-books of medicine. Where more detailed information is desired on specific topics, he may consult special monographs, in which references to key papers also are given. In spite of the appearance of a third edition, this book is not recommended. Its subject matter is presented with equal brevity and greater clarity elsewhere.

R. L. L.

#### BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Global Epidemiology. A Geography of Disease and Sanitation.* By JAMES STEVENS SIMMON, B.S., M.D., Ph.D., Dr. P.H., Sc.D. (Hon.), Brigadier General, A.U.S., TOM F. WHAYNE, A.B., M.D., Lt. Col., M.C., A.U.S., GAYLORD WEST ANDERSON, A.B., M.D., Dr. P.H., Lt. Col., M.C., A.U.S., HAROLD MACLACHLAN HORACK, B.S., M.D., Major, M.C., A.U.S., and Collaborators. Volume One: Part One—India and the Far East; Part Two—The Pacific Area. 504 pages; 26 × 18.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, \$7.00.

*Malaria: Its Diagnosis, Treatment and Prophylaxis.* By WILLIAM N. BISPHAM, Colonel, A.U.S., Retired. 197 pages; 23.5 × 16 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, \$3.50.

*The Blood Pressure and Its Disorders Including Angina Pectoris.* By JOHN PLESCH, M.D. Budapest; M.D. Berlin; L.R.C.P. and S. Edin. and Glas.; Formerly Professor of Internal Medicine in the University of Berlin. 149 pages; 22 × 14.5 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, \$4.50.

*Vital Statistics and Public Health Work in the Tropics.* By P. GRANVILLE EDGE, Lecturer in the Division of Epidemiology and Vital Statistics, London School of Hygiene and Tropical Medicine (University of London). Foreword by MAJOR GREENWOOD, D.Sc., F.R.C.P., F.R.S. 188 pages; 22 × 14.5 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, \$5.00.

*Diseases of the Digestive System.* Second Edition. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P. 932 pages; 24 × 16 cm. 1944. Lea & Febiger, Philadelphia. Price, \$11.00.

*The Urinary Tract. A Handbook of Roentgen Diagnosis.* By H. DABNEY KERR, M.D., and CARL L. GILLIES, M.D. 320 pages; 21 × 14.5 cm. 1944. The Year Book Publishers, Inc., Chicago. Price, \$5.50.

*Economy in the Use of Drugs in War-Time.* Revised Second Edition. With an Appendix on Economy in the Use of Bactericides. Medical Research Council War Memorandum No. 3. 16 pages; 24.5 × 15.5 cm. 1944. His Majesty's Stationery Office, London. Price, \$10.

## COLLEGE NEWS NOTES

### ADDITIONAL A.C.P. MEMBERS IN THE ARMED FORCES

Previously reported in the News Notes section of this journal were the names of 1,715 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,717:

Andrew M. Babey  
C. P. Rhoads

---

### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

#### *Book*

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—“Simplified Diabetic Management,” Fourth Edition.

#### *Monograph*

Dr. Richard D. Kepner, F.A.C.P., Honolulu, T. H.—“Mental Changes After Bilateral Prefrontal Lobotomy.”

#### *Reprints*

Philip K. Arzt (Associate), Lieutenant, (MC), AUS—1 reprint.  
Maurice Eliaser, Jr. (Associate), Major, (MC), AUS—1 reprint.  
Dr. Abraham E. Jaffin, F.A.C.P., Jersey City, N. J.—1 reprint.  
Dr. Josephine C. Lawney, F.A.C.P., New York, N. Y.—1 reprint.  
Dr. D. O. N. Lindberg, F.A.C.P., Wabasha, Minn.—1 reprint.  
Dr. Abraham M. Litvak, F.A.C.P., Brooklyn, N. Y.—2 reprints.  
Dr. John H. Musser, F.A.C.P., New Orleans, La.—A group of 23 reprints by members of the faculty of Tulane University, many of whom are members of the College.  
Dr. William H. Ordway, F.A.C.P., Mount McGregor, N. Y.—2 reprints.  
Dr. Aaron Parsonnet, F.A.C.P., Newark, N. J.—3 reprints.  
Dr. Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—1 reprint.  
Dr. Manuel de la Pila Iglesias, F.A.C.P., Ponce, Puerto Rico—1 reprint.  
Dr. Albert H. Rowe, F.A.C.P., Oakland, Calif.—1 reprint.  
Dr. Leon Scharitz, F.A.C.P., Philadelphia, Pa.—1 reprint.  
Dr. Maurice S. Segal, F.A.C.P., Boston, Mass.—1 reprint.  
Dr. James F. Slowey (Associate), Cleveland, Ohio—1 reprint.  
Dr. Frederick G. Speidel, F.A.C.P., Louisville, Ky.—1 reprint.  
Dr. Frederick R. Taylor, F.A.C.P., Winston-Salem, N. C.—1 reprint.  
Gilman R. Tyler (Associate), Major, (MC), AUS—1 reprint.  
Dr. Michael Weingarten (Associate), New York, N. Y.—2 reprints.

---

### NEW LIFE MEMBERS

The following physicians have recently become Life Members of the College through subscription to the permanent Endowment Fund of the American College of Physicians:

James Roderick Kitchell, F.A.C.P., Philadelphia, Pa.  
Moise D. Levy, F.A.C.P., Houston, Tex.  
T. C. Terrell, F.A.C.P., Fort Worth, Tex.

---

#### A.C.P. REGIONAL MEETINGS

A combined Regional Meeting of the American College of Physicians for Idaho, Oregon, Washington, Alberta, British Columbia, Manitoba and Saskatchewan, and the War-Time Graduate Medical Meetings was held in Vancouver, B. C., September 14-15, under the chairmanship of Dr. George F. Strong, Regent. The scientific papers were of unusually high quality, and the most dramatic and perhaps most interesting event was the attendance of Commander C. M. Wassell, (MC), USNR, the internationally famous doctor whose gallant and heroic work President Roosevelt described in such glowing terms, and whose courage and devotion will never be forgotten in the annals of military medicine. There were in attendance 96 Service physicians from the United States and Canada, and 102 civilian physicians, or a total of 198 registered. Seven states of the United States and five Provinces of Canada were represented.

At Omaha, Nebr., October 23-27, the Omaha Mid-West Clinical Society held its annual meeting, which by arrangement with the American College of Physicians, the American College of Surgeons and the War-Time Graduate Medical Meetings, was a combined, coöperative effort. Members of the two Colleges and all medical officers in the state of Nebraska and neighboring States were invited to participate. On October 26, Dr. Malcolm T. MacEachern, F.A.C.P., Associate Director of the American College of Surgeons, spoke on "The American College of Surgeons' Program for the Expansion of Graduate Training in Surgery" and Mr. E. R. Loveland, Executive Secretary of the American College of Physicians, spoke on "The American College of Physicians—Its Aims, Standards and Activities."

A Regional Meeting for the territory embracing Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin was held at the Drake Hotel, Chicago, November 4, under the general chairmanship of Dr. Walter L. Palmer, Governor for Northern Illinois, and with the participation of the College Governors for the States represented. This Regional Meeting program also formed a part of the concluding day of the American College of Physicians' Postgraduate Course, Special Phases of Internal Medicine, held at the Northwestern University Medical School, October 23-November 4, under the directorship of Dr. Willard O. Thompson.

On November 11, at Pittsburgh, a Regional Meeting of the College for the states of Ohio, West Virginia and Western Pennsylvania was held at the William Penn Hotel, under the general chairmanship of Dr. R. R. Snowden, Governor for Western Pennsylvania, with the coöperation of Dr. A. B. Brower, Dayton, Governor for Ohio, Dr. Walter E. Vest, Huntington, Governor for West Virginia, and Dr. D. A. MacGregor, Wheeling, Deputy Governor for West Virginia.

Several regional meetings of the College are planned for the future, including one in Philadelphia on December 15, under the general chairmanship of Dr. Thomas M. McMillan, Acting Governor for Eastern Pennsylvania, for the territory embracing Eastern Pennsylvania, New Jersey and Delaware; one in Memphis, Tennessee, during January, under the general chairmanship of Dr. W. C. Chaney, Governor for Tennessee, and embracing the territory of Tennessee, Arkansas, Eastern Texas, Louisiana and Mississippi; one in Oklahoma City, February 22, 1945, under the general chairmanship of Dr. Lea A. Riely, Governor for Oklahoma, and embracing the states of Oklahoma, Western Texas, Kansas and Missouri.

## A.C.P. POSTGRADUATE COURSES

The American College of Physicians conducted six postgraduate, refresher courses during the current autumn, beginning on October 2 and extending through December 15.

Course No. 1, Cardiology, at the Massachusetts General Hospital, Boston, under the direction of Dr. Paul D. White, was oversubscribed by more than four times its capacity of accommodations. There were in attendance 44 Fellows and 14 Associates, and 13 Non-members, making a total of 71. Of this number, 61 were civilian physicians and 10 were medical officers from the Armed Forces. Twenty-two States and the Dominion of Canada were represented. The largest number from any state was 12 from Pennsylvania.

With the exception of Course No. 2, General Medicine, at the University of Oregon, and Course No. 3, Special Phases of Internal Medicine, at the University of Minnesota, which had representative registrations, all courses were oversubscribed. The organization of these refresher courses has been characterized by many as one of the most important and valuable activities of the College.

---

Lt. Col. Charles H. A. Walton, F.A.C.P., retired from active duty in the Royal Canadian Army Medical Corps, September 7, 1944, and has returned to practice in Winnipeg, Manitoba.

---

REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

## General Fox Receives Typhus Commission Medal

Brigadier General Leon A. Fox, F.A.C.P., has been awarded the Typhus Commission Medal for "exceptionally meritorious service rendered first as Director and later as Field Director of the United States of America Typhus Commission." General Fox directed the Typhus Control Project of Naples in December, 1943, which brought the epidemic in southern Italy under control within a month.

## General Simmons Receives Honorary Degree from Marquette

Brigadier General James S. Simmons, F.A.C.P., Chief of the Preventive Medicine Service, Office of The Surgeon General, received the honorary degree of Doctor of Science and delivered the commencement address at the graduation exercises of the School of Medicine, Marquette University, Milwaukee, Wis., on September 27. Prior to the graduation, he addressed the Milwaukee Medical Society and the student body of Marquette Medical School on the subject of "Progress of the Army's Fight Against the Insects."

## General Morgan Speaks on Penicillin

Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant of Medicine, Office of The Surgeon General, spoke on penicillin at a combined meeting of the Kentucky State Medical Association and the War-Time Graduate Medical Meetings at Lexington, Ky., September 19.

## Communicable Diseases Figuring Prominently in the Present War

Meningococcal meningitis: As in the civilian population, this disease reached a prevalence several times higher than the normal inter-epidemic level in 1943; however, its prevalence has been somewhat lower than in the last war and its mortality, thanks to the sulfonamides, has been only a small fraction of that in the last war (case fatality rate 4.5% in 1943 as against 34.3% in 1917-1919).

Primary atypical pneumonia: Comparison with previous periods is impossible as this disease has only recently been recognized clinically. There is evidence that more of the pneumonias now occurring are primary atypical than of known bacterial etiology. The case fatality rate has been very low. The disease has had a seasonal distribution similar to that of the common respiratory diseases.

Diarrheal diseases: This group of diseases of diverse etiology, but having a common basis in deficiencies of sanitation, has shown a considerable increase from peacetime owing to the much greater number of troops on maneuvers, especially during the summer months, with the added problems of field sanitation. Case fatality is very low. The present trend of rates is downward.

With respect to other communicable diseases too, the record has been excellent. Measles, mumps and scarlet fever are reduced greatly, while diseases against which immunizing methods are practised (typhoid, smallpox, tetanus) have all but disappeared.

#### Recent Promotions

Lieutenant Colonel to Colonel

Irving Sherwood Wright, F.A.C.P., New York, N. Y.

Major to Lieutenant Colonel

Howard Phelps Lewis, F.A.C.P., Portland, Ore.

Walter L. Nalls, F.A.C.P., Richmond, Va.

#### Nutrition Consultants Appointed

Dr. Julian M. Ruffin, F.A.C.P., Associate Professor of Medicine, Duke University, Durham, N. C., and Dr. Virgil P. Sydenstricker, F.A.C.P., Professor of Medicine, University of Georgia, Augusta, Ga., have been appointed Consultants to the Surgeon General in the field of nutrition.

---

Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, and his associates, received the first award of merit for an exhibit on pituitary irradiation at the meeting of the American Roentgen Ray Society at Chicago recently.

---

Dr. William G. Leaman, Jr. F.A.C.P., Professor of Medicine at the Woman's Medical College of Pennsylvania, Philadelphia, has deposited in the files of the American College of Physicians a catalogue of the lantern slides collection of that Institution. There are 4,117 slides, both standard size (3¼" × 4") and small size (2" × 2") in the collection of the Department of Medicine. Many of the small size films are Kodachrome. These slides are made available to any speaker on a College program in an emergency.

The Woman's Medical College of Pennsylvania is conducting its second annual postgraduate lecture course, given by the Department of Medicine, from September 27, 1944, through April 19, 1945. The classes meet from 7:00 to 9:00 p.m. This year's course will be devoted to clinical topics. Speakers have been chosen from the faculties of various medical schools in Philadelphia. The object of the course is to present to the general practitioner the recent advances in the field of internal medicine. Enrollment is limited to fifty and the fee for the entire year is \$25.00.

---

Dr. L. B. Carruthers, F.A.C.P., Professor of Medicine and Dean of the Miraj Christian Medical School, Miraj, India, has recently been made a Member of the Royal College of Physicians of London.



Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, recently received the Decoration of the Heraldic Order El Sol Del Peru in the class of Knight Commander by His Excellency, the President of Peru. The citation reads:

"As President of the San Francisco Chapter, Pan American Society, Dr. J. C. Geiger has aided materially in fostering and cementing friendly relations between countries of the Americas; as a teacher of preventive medicine and public health in universities, medical officer of health and chief of hospitals, he has added much to the glorious chapter of the prevention of disease."

Dr. Geiger made the commencement address at Tulane University School of Medicine on October 14, 1944, the largest commencement in the history of that University. Dr. Geiger was given the honorary degree of Doctor of Science, which was the second honorary degree to be conferred upon him by Tulane University. It is said that this is Dr. Geiger's fifth degree from Tulane and his seventh honorary degree from this and other universities.

Major Winthrop Wetherbee, Jr., F.A.C.P., was recently transferred from the Seventh General Hospital to the 116th General Hospital, overseas, as Chief of Medical Service.

Lt. Col. Joseph Hayman, F.A.C.P., has recently been placed in charge of a newly established special treatment center for malaria and other tropical diseases at the Moore General Hospital, Swannanoa, N. C.

On September 22, 1944, Dr. Herbert T. Kelly, F.A.C.P., Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, presented before the session on Nutrition of the Pennsylvania Nutrition Council and State Council of Defense, at Harrisburg, Pa., a paper on "Conservation of Human Resources."

#### NEW JOURNAL OF PARENTERAL THERAPY ESTABLISHED

Publication of a new quarterly, the Journal of Parenteral Therapy, has been announced by Science Publications Council, New York. The Advisory Editorial Board includes the following physicians and surgeons: W. Wayne Babcock, Philadelphia; I. A. Bigger, Richmond, Va.; Alexander W. Blain, Detroit; Frederick A. Collier, Ann Arbor, Mich.; Joseph H. Fobes, New York; Henry N. Harkins, Baltimore; Lester Hollander, Pittsburgh; Alton Ochsner, New Orleans; Max M. Strumia, F.A.C.P., Bryn Mawr, Pa.; George J. Thomas, Pittsburgh. Justus J. Schifferes, New York, is managing editor.

The Mississippi Valley Medical Society held its tenth annual meeting at Peoria, Ill., September 27-28. Among contributors to the program were: Dr. A. C. Ivy, F.A.C.P., Chicago, "The Rationale of Tests of Liver Function"; Dr. Willard O. Thompson, F.A.C.P., Chicago, "The Fröhlich Syndrome"; Dr. Edwin C. Ernst, F.A.C.P., St. Louis, "Diagnosis and Treatment of Cancer of the Cervix"; Dr. O. P. J. Falk, F.A.C.P., St. Louis, "Practical Points in Recognition and Management of Coronary Diseases"; Dr. R. O. Muether, F.A.C.P., St. Louis, "Round Table Discussion on Hypertension."

"Pathology of Internal Medicine" is the title of a postgraduate course scheduled at the Israel Zion Hospital, Brooklyn, which began on October 17, and will be conducted by Dr. Jacob M. Ravid (Associate), under the auspices of the Joint Committee on Postgraduate Education of the Long Island College of Medicine, the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn. The course is designed to familiarize the internist as well as the general practitioner with the fundamentals of gross and microscopic pathology of internal medicine. Great stress will be laid on gross pathological diagnosis of tissues and organs.

---

The International College of Surgeons, United States Chapter, was addressed at its Philadelphia National Assembly, October 3-5, by Dr. George Morris Piersol, F.A.C.P., Director of the Center for Research in Physical Medicine, University of Pennsylvania, on "Rehabilitation"; Dr. Charles M. Griffith, F.A.C.P., Washington, Medical Director of the Veterans Administration, spoke on "The Rehabilitation of Ex-Members of the Armed Forces by the Veterans Administration"; Dr. Truman G. Schnabel, F.A.C.P., Clinical Professor of Medicine at the University of Pennsylvania, spoke on "The Everpresent Post-Operative Respiratory Complications."

---

The New York Academy of Medicine conducts a Friday evening lecture series from November through April. On December 8, Dr. Emanuel Libman, F.A.C.P., will deliver an address on "Diagnostic Observations on Abdominal Diseases," and on January 12, Dr. H. McLeod Riggins, F.A.C.P., will deliver an address on "Present Trends in the Treatment of Pulmonary Tuberculosis."

---

#### FELLOWS OF THE COLLEGE SERVING AS CHAIRMEN OF SECTIONS, A.M.A.

Dr. William D. Stroud, F.A.C.P., Philadelphia, is serving as Chairman of the Section on the Practice of Medicine, and Dr. Louis H. Clerf, F.A.C.P., Philadelphia, is serving as Chairman of the Section on Laryngology, Otology and Rhinology, for the current year.

---

Dr. O. H. Perry Pepper, Captain Edward L. Bortz, (MC), USNR, and Dr. William D. Stroud, all of Philadelphia, are Fellows of the College who are among the foreign corresponding members of the Society of Internal Medicine of the Medical Association of Argentina.

---

Major General Charles R. Reynolds, F.A.C.P., U. S. Army retired, has resigned as Chief of the Division of Tuberculosis of the State Department of Health of Pennsylvania, to accept an appointment with the American College of Surgeons in Chicago. General Reynolds was Surgeon General of the U. S. Army from 1935-39.

---

Dr. Frank R. Menagh, F.A.C.P., and Dr. Clarence E. Reyner, F.A.C.P., both of Detroit, are President and Secretary-Treasurer, respectively, of the Detroit Dermatological Society.

---

Dr. Benjamin A. Shepard, F.A.C.P., because of ill health, has resigned as President of the Kalamazoo Tuberculosis Association.

---

Dr. Wallace E. Herrell, F.A.C.P., Rochester, Minn., addressed the Medical Society of Virginia at its annual meeting in Richmond, October 23-25, on "Penicillin."

Ernest L. Boylen, F.A.C.P., Major, (MC), AUS, formerly of Portland, Ore., has been awarded the Bronze Star for meritorious service in direct support of combat operations in Italy last December and January.

---

The Northwestern Ohio Medical Society observed its 100th anniversary at Findlay, Ohio, October 3. Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., addressed the luncheon meeting on "Hints in the Recognition of Puzzling Abdominal Pain." Other speakers included the following members of the faculty of the University of Cincinnati College of Medicine: Dr. M. A. Blankenhorn, F.A.C.P., "The Toxic Reactions of the Newer Sulfonamides"; Dr. Leon Schiff, F.A.C.P., "Tests of Liver Functions in Health and in Disease."

---

Dr. John A. Toomey, F.A.C.P., Cleveland, was a guest speaker at the 55th annual meeting of the American Pediatrics Society, Atlantic City, September 26-27, his title being "Attempts to Isolate Poliomyelitis Virus in Fish."

---

The late Dr. Charles Hartwell Cocke, F.A.C.P., Asheville, provided in his will that his medical library, magazines and other publications be given to the Buncombe County Medical Society Library in Asheville. Dr. Cocke died on August 3.

---

Dr. Tom D. Spies, F.A.C.P., Birmingham and Cincinnati, was a guest speaker at the 79th annual session of the Michigan State Medical Society at Grand Rapids, September 27-29, his subject being, "Vitamins and the Practice of Medicine." Among military speakers on the program were Brigadier General Charles C. Hillman, F.A.C.P., "Tropical Medicine"; Colonel William C. Menninger, F.A.C.P., "Neuropsychiatry and the General Practitioner"; Brigadier Jonathan C. Meakins, F.A.C.P., Montreal, "What a Modern Army Health Service Should Be."

---

Colonel Neely C. Mashburn, F.A.C.P., has been appointed Surgeon at the AAF Training Command, Fort Worth, Tex.

---

Dr. Hugh H. Hussey, Jr., F.A.C.P., has been named Chairman and Dr. Roy L. Sexton, F.A.C.P., has been named a member of a medical advisory committee appointed by the District of Columbia Office of Price Administration to pass on all applications for extra food rations for convalescents and persons in ill health.

---

Dr. Thomas N. Hunnicutt, Jr., F.A.C.P., Newport News, Va., has been elected President of the Warwick County Medical Society.

---

Dr. Alfred Meyer, F.A.C.P., New York City, is probably the oldest physician among Fellows of the American College of Physicians; aged 90, born in 1854. Although now retired, Dr. Meyer keeps up an active interest in medicine. He received his B.A. from Columbia University in 1874 and his Medical Degree from the College of Physicians and Surgeons, Columbia University, in 1877. He did extend post-graduate study at the University of Leipsic, at the University of Vienna and in hospitals of London, Paris and Rome. He has had a distinguished career, has published many contributions to the literature, and has been a Fellow of the American College of Physicians since 1919.

## WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 1 (Maine, New Hampshire, Vermont, Massachusetts) and REGION No. 2 (Connecticut, Rhode Island)—New England Committee for War-Time Graduate Medical Meetings—Dr. W. R. Ohler, Chairman; Dr. L. E. Parkins, Secretary.

*Station Hospital, Dow Field, Bangor, Maine*

December 21 Head, Spine and Nerve Injuries

*Dispensary, U. S. Naval Air Station, Brunswick, Maine*

December 21 Burns and Reconstruction Surgery

*Station Hospital, Fort Williams, Portland, Maine*

December 21 The Skin

*Station Hospital, Presque Isle, Maine*

December 21 Stomach, Biliary Tract, Intestinal Disorders

*Dispensary, U. S. Naval Construction Training Center, Quoddy Village, Maine*

December 21 Pilonidal Sinus and Common Diseases of the Anus and Rectum

*Station Hospital, Grenier Field, Manchester, New Hampshire*

December 20 Peripheral Vascular Disease

*U. S. Naval Hospital, Portsmouth, New Hampshire*

December 21 Diarrheal Diseases

*Boston Area Station Hospital, Waltham, Massachusetts*

December 21 The Use of Penicillin and the Sulfa Drugs

*U. S. Naval Hospital, Chelsea, Massachusetts*

December 21 Blood Dyscrasias and Transfusions

*Lovell General Hospital, Fort Devens, Massachusetts*

December 21 The Pneumonias and Other Respiratory Infections

*Station Hospital, Camp Edwards, Massachusetts*

December 21 The Psychoneuroses and Their Management

*Cushing General Hospital, Framingham, Massachusetts*

December 21 Contagious Diseases and Complications

*Station Hospital, Camp Myles Standish, Taunton, Massachusetts*

December 21 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

*U. S. Marine Hospital, Brighton, Massachusetts*

December 21 Acute Infections of the Central Nervous System

*Station Hospital, Westover Field, Chicopee Falls, Massachusetts or U. S. Naval  
Convalescent Hospital, Springfield, Massachusetts*

December 21 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

*Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island*

December 21 Joint Injuries

*U. S. Naval Hospital, Newport, Rhode Island*

December 21 Fractures of Extremities

*Station Hospital, Bradley Field, Windsor Locks, Connecticut*

December 21 Fractures of Extremities

*Air Corps Station Hospital, New Haven, Connecticut*

December 21 Chest and Abdominal Injuries

*Station Hospital, Fort H. G. Wright, Fishers Island, New York*

December 21 Acute Abdominal Emergencies

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr.  
N. C. Gilbert, Dr. W. H. Cole.

*Station Hospital, Camp McCoy, Wisconsin*

November 29 Endocrinology

- a. Addison's Disease
- b. Adrenal Cortex in Shock
- c. Parathyroid Tetany
- d. Traumatic Hypogonadism
- e. Hypothyroidism
- f. Hyperthyroidism
- g. Post Traumatic Pituitary Syndrosis

—Dr. Elmer L. Sevringhaus

December 13 Virus and Rickettsial Diseases

- a. Virus Diseases
- b. Rickettsial Diseases

—Dr. Marcos Fernan-Nunez

*Station Hospital, Truax Field, Wisconsin*

November 29 Gall Bladder and Liver Disease

- a. Mechanism of Liver Function

Diagnosis and Medical Treatment of Liver and Gall  
Bladder Disease

- b. Surgical Pathology and Treatment

—Dr. E. R. Schmidt

December 13 Thrombosis, Thrombophlebitis and Anticoagulants

- a. Thrombosis, Thrombophlebitis and Embolism  
Diagnosis and Treatment

- b. Heparin and Dicoumarol

Action and Therapeutic Use

—Dr. Armand J. Quick

Note: War-Time Graduate Medical Meetings at Camp McCoy and Truax Field are arranged by the coöperating committee for Wisconsin. The members of this committee are Dr. Erwin R. Schmidt, Chairman; Dr. Elmer Sevringhaus and Dr. Francis D. Murphy.

---

#### DIRECTORY OF MEDICAL SPECIALISTS

The biographic data of the first two editions of the Directory of Medical Specialists included only positions (internships, residencies, or assistantships) held during the course of training of men up to the time of their certification by the American Boards, and hospital and medical school staff positions then currently held.

It is desired to extend these data in the Third Edition to include all formal hospital and medical school appointments, with dates held, even though now resigned, as well as records of all military service including commissions and dates, either in World War I, peace-time in the Reserve forces, or in the present war.

Thus, a chronologically complete sketch of a Diplomate's entire career is to be included in this Third Edition of the Directory.

Membership or fellowship in national or sectional (not local) special societies, and national general societies with offices held, and dates, in any of these, should be reported.

Membership in recognized international medical societies may be included, but honorary or other membership in foreign medical societies should not be reported.

Reference to the Second Edition (1942) of the Directory may be made for lists of medical societies to be included in one's biographic sketch.

Families or secretaries of men absent in military service are asked to complete or correct previous listings on new forms now being mailed to those eligible for inclusion in the Directory. Only those certified by an official American Board can be included, and there is no charge for this listing.

The foregoing notice is published in response to many inquiries, to assist those certified by the American Boards who are now engaged in correcting their previous listings, or preparing new sketches for the Third Edition of the Directory to be published early in 1945.

Communications should be addressed to the Directory of Medical Specialists, 919 North Michigan Avenue, Chicago 11, Illinois.

---

Dr. Walter A. Bastedo has called attention to an error occurring on page 507, *ANNALS OF INTERNAL MEDICINE*, September, 1944. He writes: "The New York Academy of Medicine Committee on Drug Exhibits is composed of Drs. Arthur DeGraff, Cary Eggleston, Harry Gold, Charles C. Lieb and George Wallace, with the writer (Walter A. Bastedo) as Chairman. This Committee has as its object the maintenance of a continuous exhibit of the newer remedies, which shall be scientific, educational and non-Commercial.

"As an auxiliary to this Committee an Advisory Committee of Drug Manufacturers was formed with Dr. Theodore G. Klumpp as Chairman."

## OBITUARIES

## DR. JOHN THOMAS MURPHY

Dr. John Thomas Murphy, F.A.C.P., died on the 15th day of June, 1944, at the age of 58. He had just completed his thirty-eighth year of medical practice, having graduated in medicine at the early age of 21.

He received his degree of Doctor of Medicine from the University of Toledo in 1906. In 1907 he was instructor in Histology in this university and during the following two years, 1908-09, an instructor in Pathology. His interest in these fields persisted throughout his life.

Through the hobby of photography he was led into his chosen field of roentgenology. His early training in this new specialty was obtained in Cook County Hospital in Chicago. He was appointed to the directorship of the Radiological Department of St. Vincent's Hospital in Toledo in 1917, a position which he held until his death.

In medicine, as in all of his interests, his prime motive was to determine the basic facts. It was this constant search for the truth, with a total abhorrence of half truths, that made him an outstanding man in whatever he undertook and placed him among the leaders of roentgenology.

In play, as in work, John Murphy expended his full energy. As a boy and young man he excelled in athletics, especially track. Ice skating was a hobby which held his interest throughout life. His experiences in early flying were always a source of satisfaction to him and later stimulated him to take an interest in other young men who were similarly inclined. Thus came the inspiration to start, along with other Toledo persons, the Civil Air Reserve.

To few men are given the qualities of attraction and endearment which Dr. Murphy possessed. Many honors were bestowed upon him, yet he remained modest and unaffected.

Dr. Murphy was a member and past president of the Academy of Medicine of Toledo and Lucas County; member of the Ohio State Medical Association; member of the American Medical Association and secretary of its Radiological Section from 1931 until his death; past president of the Detroit Roentgen Ray Society; charter member of the Ohio State Radiological Society; secretary of the American Roentgen Ray Society, 1928-31, president 1934; member of the American Radium Society; member of the Radiological Society of North America; president of the American College of Radiology in 1935; fellow of the American College of Physicians.

With the passing of this man organized medicine has lost an energetic champion, the community a faithful citizen, his friends and associates a wise and sympathetic counsellor, his family a generous and devoted father and his patients a good physician.

C. E. HUFFORD, M.D., F.A.C.P.,  
Toledo, Ohio

## DR. GROESBECK FRANCIS WALSH

Dr. Groesbeck Francis Walsh, (F.A.C.P.), Fairfield, Alabama, died September 1, 1944, of carcinoma of the urinary bladder. Dr. Walsh, who had been a Fellow of the College since 1931, was born in Chicago, Illinois, March 31, 1878. He received his A.B. degree in 1898 from St. Ignatius College (now Loyola University, Chicago) and his M.D. from Northwestern University Medical School in 1902. He was engaged in post-graduate study at Leland Stanford University in 1912 and 1913. He was First Assistant, Surgical Clinic, Colon Hospital, Canal Zone, 1907-10; Health Officer, Republic of Nicaragua, 1908; and Chief of Surgical Staff, Candelaria Hospital, Amazonas, Brazil, 1910-11. In 1919 Dr. Walsh became Chief of Medical Clinic, Employees' Hospital of the Tennessee Coal, Iron and Railroad Company, and remained in that position until his death. He was a member of the American Public Health Association, American Trudeau Society, American Association of Industrial Physicians and Surgeons, American Association for the Advancement of Science, Alabama Academy of Science, Jefferson County Medical Society, Alabama State Medical Association, Southern Medical Association, and Birmingham Clinical Club; Fellow, American Medical Association. He was former President (1932-34) of the Southern Interurban Clinical Club and Diplomate of the American Board of Internal Medicine. Dr. Walsh served in World War I as Chief of Laboratory Division, Naval Operating Base, Hampton Roads, Virginia, and in the Transport Service, U.S.S. Orizaba.

Dr. Walsh was a keen clinician and was much interested in the psychosomatic side of medical practice. In recent years the subject of handedness intrigued him greatly and he delved deeply into both lay and medical literature in research along this line, finding in Shakespeare particularly many references to left handedness. He was the author of many published papers. Dr. Walsh was a great lover of flowers, with a wide knowledge of horticulture. He was a wise counsellor, most attractive personally and greatly beloved by many friends. He will be sadly missed in the medical profession of Alabama.

FRED W. WILKERSON, M.D., F.A.C.P.,  
Governor for Alabama

## DR. ANDREW PORTER BIDDLE

Dr. Andrew Porter Biddle, F.A.C.P., was born in Detroit, February 25, 1862, and died in the city of his birth August 2, 1944, at the age of 82.

His primary and secondary education in the public schools of Grosse Ile and Detroit was supplemented by special studies in Geneva, Switzerland, Heidelberg, and Leipzig, Germany. He received an appointment as cadet and entered the United States Naval Academy in 1880, but later had to withdraw because of a visual impairment. He then entered the Detroit College of Medicine where he received the degree of Doctor of Medicine in 1886.



Dr. Biddle's services to his profession, and to the community in which he lived were legion. Space permits mention here of only a few of the more outstanding: Professor of Dermatology at his Alma Mater; Consultant, St. Mary's, St. Joseph's Mercy, Children's, and Woman's Hospitals, and Detroit Board of Health; First President, Detroit Dermatological Society, 1922, and President of American Dermatological Association, 1925-26; Formerly Secretary, Councillor and President of the Michigan State Medical Society, the only member ever to be honored with two successive terms as President during the eighty years of the Society's existence; Co-organizer and first Editor of the Journal of the Michigan State Medical Society, a position which he held for four years; former Secretary of Wayne County Medical Society; for many years member of the Detroit Library Commission and of the Detroit Board of Education, becoming President of this body.

In recognition of these splendid services and of Dr. Biddle's sterling worth as a man the following honors have been bestowed upon him: Doctor of Science, honorary, College of the City of Detroit, 1929; Master of Science, honorary, University of Michigan, 1935; Andrew P. Biddle oration established by the Michigan State Medical Society. Fitting resolutions of eulogy were passed by Michigan State Medical Society and Wayne County Medical Society and made a part of the permanent records of those societies.

Industrious and frugal during his long life, Dr. Biddle was able to make several bequests. Chief among these were bequests to Michigan State Medical Society, to the University of Michigan, and to the Detroit Library Commission. These were all made in the interest of postgraduate education, a matter that was close to his heart.

The Michigan Fellows and Associates of the American College of Physicians join his other friends in mourning the passing of a great man.

P. L. LEDWIDGE, M.D., F.A.C.P.,

Acting Governor for Michigan

### DR. JOSEPH P. TRAYNOR

Dr. Joseph P. Traynor of Natick, Mass., died September 12, 1944. He was born at Biddeford, Maine, in 1878, graduated in medicine from Bowdoin Medical School in 1901, and early in his career entered the Medical Corps of the United States Navy. During his career as a Naval Medical Officer, his assignments covered most of the important stations in the world from which the Navy operates. He did postgraduate work at the Naval Medical School and at the Massachusetts General Hospital.

Some years ago he retired from active duty and has, in the meantime, resided at Natick, Mass.

He had been a Fellow of the American College of Physicians since 1923.

## DR. JOSEPH LESLIE SHERRICK

The death of Dr. Joseph Leslie Sherrick, F.A.C.P., of Monmouth, Illinois, on July 28, 1944, is a deep loss to the community he served and to the medical profession. His thirty years of fine medical service, the wide scope of his interests, the esteem in which he and his ability were held, mark him as one who typified the ideals of The American College of Physicians. The generous living of such a man as Dr. Sherrick is one of our strongest arguments against socialized medicine.

Dr. Joseph Leslie Sherrick was born in Little York, Illinois, in 1888. He received his A.B. from Monmouth College in 1908, and his M.A. from Yale in 1910. He attended the Johns Hopkins University School of Medicine in 1914, and interned at Massachusetts General Hospital in 1914-1915. He was for many years a Member of the Staff of the Monmouth Hospital; a Trustee of Monmouth College; Associate Medical Director of the Illinois Bankers Life Assurance Company; Director of the Second National Bank of Monmouth; Member of The Warren County Medical Society; Member of the Illinois State Medical Society; Fellow of The American Medical Association, and Fellow of The American College of Physicians since 1926. He died July 28, 1944, at the age of 56.

Dr. Sherrick was physician for the C. B. & Q., and the M. & St. Louis Railroads. He was resident physician for Monmouth College for Women, and for the past year and a half has been civilian physician for the Naval Flight Preparatory School at the College. He has served as Internist on the Medical Advisory Board No. 16 of the Selective Service for the past three years. He was a member of Monmouth Lodge No. 37 A.F. and A.M. and of the First United Presbyterian Church. He was Secretary of the Monmouth Medical Club for twenty years, also Secretary of The Monmouth Hospital Staff for the same number of years.

Dr. Sherrick's father was a physician in Monmouth and died two years after his son joined him in practise there. Their combined service to the community extend over almost fifty years. He is survived by his wife and two sons, First Lieut. Joseph C. Sherrick, M.D., now stationed at Carlisle Barracks, Pa., and John M. Sherrick, a chemist in Chicago, Illinois.

His death followed an attack of acute respiratory disease which had confined him to his bed for several weeks. Our untimely loss of Dr. Sherrick when he was in the midst of all his valuable services can be recorded as another war casualty.

CECIL M. JACK, M.D., F.A.C.P.,  
Governor Southern Illinois

## DR. FOSTER LEONARD DENNIS

Dr. Foster Leonard Dennis, F.A.C.P., Dodge City, Kansas, was born in Potawatomie County, Kansas, November 12, 1895. He attended the

University of Kansas for three years, and then transferred to St. Louis University, from which he received his B.S. degree in 1918. He graduated in medicine from the Jefferson Medical College of Philadelphia in 1921, and thereafter spent a two-year internship at St. Mary's Hospital in Kansas City, Mo. At one time, he served as Director of the Clinical Laboratory and Instructor in Medicine and Bacteriology to the Nurses Training School, St. Anthony's Hospital, and was Chief of Staff there from 1932 to 1934. He was also Physician-in-Chief, Kansas State Soldiers' Home Hospital. Dr. Dennis was commissioned a Major in the Medical Corps, Army of United States, on February 24, 1943 and for a time was stationed at the Walter Reed General Hospital in Washington, D. C., and thereafter attached to the 22nd General Hospital.

Dr. Dennis was a member of the Kappa Sigma and Phi Chi Fraternities, and of Illustriana, a society of professional men, native born Kansans. He was a member of the Ford County Medical Society and the Kansas State Medical Society, was a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1929. He died June 26, 1944, of cerebral hemorrhage, at the age of 48. Possessed of a charming and pleasing personality, he was interested in scientific medicine, was a progressive and intelligent man, highly regarded by his fellow practitioners.

#### DR. FRANKLIN DAVIS WILSON

Dr. Franklin Davis Wilson died November 17, 1943, in Norfolk, Virginia, after many years of hard work. Dr. Wilson was born in Norfolk County, Virginia, June 8, 1882. He received the degree of Doctor of Medicine from the University of Maryland School of Medicine and College of Physicians and Surgeons in 1908. Following this, he returned to South Norfolk where he practiced until 1918 when he went to Harvard for a year and a half post-graduate study of Pediatrics. Following this period, Dr. Wilson returned to Norfolk and took up his work in the field of Pediatrics to which he contributed in many ways. Prior to graduation, Dr. Wilson had been Clinical Assistant at the University of Maryland Hospital from 1907-1908, and later, following specialization in Boston, he became a House Officer in the Children's Hospital in Boston from 1909-1920.

A long list of appointments in this field attest his service to his fellow man. Dr. Wilson was Consultant in Pediatrics at Mt. Sinai and Norfolk Memorial Hospital. Lecturer in Pediatrics at the Nurses Training School, Norfolk Protestant Hospital, Vice-President and Visiting Physician, Bonney Home for Girls; formerly, Visiting Physician, King's Daughters Children's Hospital; member of the Norfolk County Board of Health, 1916-1918; formerly member of the Norfolk Council of Social Agencies and of the Norfolk County School Board; formerly President and Visiting Physician of

the Norfolk Society for the Prevention of Cruelty to Children. He was the author of numerous publications dealing with Child Health and Welfare.

In addition to these appointments, he was former President of the Norfolk County Medical Society and the Virginia Pediatric Society; also member of the Medical Society of Virginia, American Academy of Pediatrics, the Southern Medical Association, American Medical Association, Tri-State Medical Society of Carolina and Virginia, and the Seaboard Medical Society, as well as a Fellow of the American College of Physicians since 1931.

Dr. Wilson was a man of deep religious convictions and a member of the Society of Friends. His quiet, determined efforts were devoted largely to the problems of children and child welfare. His efforts in the field of children's work were not limited to the Norfolk area as he served on the Child Welfare Committee of the State of Virginia since 1933, having been Chairman since 1936. He leaves his wife, a son, and two daughters.

J. EDWIN WOOD, JR., M.D., F.A.C.P.,  
Governor for Virginia

#### DR. ROBERT L. CUNNINGHAM

Dr. Robert L. Cunningham, F.A.C.P., Los Angeles, Calif., died suddenly at his home on September 10, from his second attack of coronary thrombosis. The first attack occurred more than 10 years ago.

Dr. Cunningham was born at Shushan, New York, in 1880. His school days were spent in Indiana, and he obtained his A.B. degree at Wabash College in 1901. He received his medical training at Johns Hopkins University School of Medicine, graduating in 1907 and remaining there as interne the following year. He went west after completing his internship and began to practise as an internist in Los Angeles, California, devoting himself especially to the study of diseases of the lung. He became a well-known figure at the Barlow Sanitarium as attending physician from 1911 until the time of his death. He became, successively, President of the Los Angeles Tuberculosis Association from 1930-1933 and of the California Tuberculosis Association in 1934. For many years he was Clinical Professor of Medicine at the University of Southern California School of Medicine, member of the staff of the Hospital of the Good Samaritan, and consulting physician at the Children's Hospital and St. Vincent's Hospital.

Dr. Cunningham was a past president of the Los Angeles Academy of Medicine, a member of the Los Angeles County Medical Society, the California State Medical Association, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1927. His death means a great loss to his friends and the entire medical profession of Southern California.

ROY E. THOMAS, M.D., F.A.C.P.,  
Governor for Southern California

## DR. MALCOLM GRAEME MacNEVIN

Dr. Malcolm Graeme MacNevin, F.A.C.P., San Francisco, Calif., died on a train May 21, 1944, of chronic myocarditis and coronary occlusion; aged, 78. He was born at Caledonia, Ontario, on November 23, 1865, attended the local public schools and prepared under private tutor for admission to the University of Michigan, from which he received his M.D. degree in 1890. He chose the United States for his permanent home and became a naturalized citizen. For twelve years, 1894 to 1906, he was Chief Surgeon, St. James Hospital, Butte, Mont. However, he became interested in gastroenterology and problems of nutrition, and made these his special field of endeavor for the balance of his life.

Dr. MacNevin did postgraduate work at Guys Hospital and the London Hospital of England, and at the University of Berlin in Germany. Between his work in Butte, Mont., and his going to San Francisco, he spent a considerable period of time in New York City, where he was Assistant Professor of Medicine and Chief of the Medical Clinic at the New York Post Graduate Medical School and Hospital; also Attending Physician at St. Barnabas Hospital and Consulting Gastro-enterologist at the Hospital for Ruptured and Crippled. In 1931 he became attached to the Southern Pacific Hospital at San Francisco, which appointment he held to the time of his death. He had been a Fellow of the American College of Physicians since 1929.

## DR. FRANCIS PATRICK McNAMARA

Dr. Francis Patrick McNamara, F.A.C.P., Dubuque, Iowa, died July 2, 1944, aged 59. He was born at Fitchburg, Mass., December 22, 1884. He graduated from Harvard Medical School in 1918, and thereafter did postgraduate work in Pathology and Bacteriology at Yale University, and Biochemistry at Harvard.

He early restricted his work to the field of Pathology. He was at one time Assistant in Bacteriology, Assistant in Pathology and Instructor in Pathology at Yale University Medical School. Since 1922, he had been Pathologist at the Finley Hospital, Dubuque; Consulting Pathologist at Decorah Hospital; member of the staff, St. Joseph Mercy Hospital. Dr. McNamara was a member of the Iowa State Board of Health and served as President of the Iowa State Medical Society, 1940-41. He had also been President of the Dubuque County Medical Society. He was a Fellow of the American Medical Association, and in 1933 received its Silver Medal for a scientific exhibit illustrating the activities of the pathologic laboratory in a hundred-bed hospital. He was also a member of the American Association of Pathologists and Bacteriologists, American Society of Clinical Pathologists and the American Society for the Control of Cancer. He was a Diplomate of the American Board of Pathology, and had been a Fellow of the American College of Physicians since 1931.

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 21

DECEMBER, 1944

NUMBER 6

---

## A HIGH FLUID INTAKE IN THE MANAGEMENT OF EDEMA, ESPECIALLY CARDIAC EDEMA. II. CLINICAL OBSERVATIONS AND DATA\*

By F. R. SCHEMM, M.D., F.A.C.P., *Great Falls, Montana*

It is only in the last 50 years that the limitation of fluids in the presence of edema has been taught and practiced so universally. Earlier clinicians noted that the theoretical fear of water in dropsy was not justified by close bedside observation.<sup>42-45</sup>

In 1772 Sir George Baker reported that dropsy clears in patients given large amounts of water, and comments: "I much wish to see an indulgence of this kind extended to poor thirsty dropsical patients. In making such an experiment, indulge the patient to the utmost extent. A limited permission may be pernicious."

In 1777 William Withering said: "I allow, and indeed enjoin, my patients to drink very plentifully of small liquors through the whole course of the cure," and added in 1785 after citing his 163 cases, that: "This direction is the more necessary as they are very generally prepossessed with an idea of drying up a dropsy by abstinence from liquids and fear to add to the disease by indulging their inclination to drink."

In 1786 Sir Francis Millman, "lest futile and exploded theories should be set against facts and experience," cited some 40 examples and concluded: "To irritate the body with medicines and prohibit drink is prejudicial to the patient. Treatment will be much more fortunate with large and frequent draughts of diluting drink."

In 1845 John Darwell brought such observations well into the nineteenth century: "The vulgar opinion which formerly prevailed that fluids ought not to be allowed to dropsical patients (is) completely exploded, . . . the restriction from fluids is not only not beneficial but in many cases even injurious . . . much additional evidence has been obtained to the same purpose."

---

\* Received for publication December 23, 1943.

Read at the St. Paul meeting of the American College of Physicians April 22, 1942.  
From the Medical Department of the Great Falls Clinic, Great Falls, Montana.

These voices fade as fascinating new theories<sup>9</sup> about edema and congestive heart failure prevail over observed facts, although for a time Austin Flint<sup>47</sup> and Osler<sup>48</sup> repeated after Dickinson that in nephritis "Of all diuretics, water is the best." In the last decade only a few clinicians<sup>49, 50, 51, 52</sup> have seen limited or probable indications for water in edematous patients, and ideas about edema seem little affected by Newburgh's<sup>4</sup> significant observation that edema in nephritis yields to an intake as high as four liters daily.

The clinical application of his renal-function and water-balance work<sup>1, 2, 3</sup> and its extension by Collier and Maddock<sup>6, 7</sup> to surgical problems were observed at first hand by the author from 1930 to 1933. It was noted that certain of their cases had grossly abnormal hearts which tolerated large amounts of water by mouth or by vein, but that, in violation of water balance principles, other cases of *primary* cardiac disease with edema were commonly subjected to a restriction of fluids or were allowed only enough water for the relief of thirst, if they were capable of complaining of it. It appeared rational to try the effect of a high fluid régime with an actual forcing of fluids on all edematous "brine-logged" patients, especially those with cardiac disease.

#### METHOD OF STUDY

The actual clinical study was begun in 1933 in a general hospital of 200 beds, without internes or residents. The régime, as described in detail in Part I of this report,<sup>67</sup> was put in force during the periods of observation by giving:

- (1) A large Amount of Water, orally or by vein (see table 7 for amounts).
- (2) A "neutral" Diet to regulate the ingestion of sodium, to insure:
  - (a) Reduced Amounts of Salt and Sodium and a slight
  - (b) Excess of Acid-Ash. Small amounts of Acid Drugs were usually given to augment the effect of the diet. (See table 2 for the individual importance of the amount of water, amount of sodium, and the diet reaction.)

*Other therapy* was determined by the primary disease. When compatible with the safety of the patient, digitalis, mercurial diuretics, and even acid drugs were withheld until the edema cleared; thyroid extract and vitamin B were given only after edema had disappeared; acacia, hypertonic solutions and aminophyllin were not given. The diet protein was sometimes reduced from 65 to 40 grams daily until edema had cleared.

*Clinical Data.* (1) The *history* included the recording of immediate prior therapy, especially (a) the amount of rest, digitalis, oxygen, acid drugs and mercurial diuretics; (b) the size of the fluid intake; (c) the amount of salt or basic-ash foods in the diet.

(2) The *examination* for the status of the edema was usually made every morning: (a) puffiness, fullness, and the presence and depth of pitting over the periphery of the body from face to feet, especially posteriorly, were noted; (b) the level of hydrothorax and distribution and level of râles over the lung fields; (c) the level of the liver edge, signs of free fluid, and the degree of fullness and tension of the abdomen were recorded.

(3) *Water balance data*, incomplete but practical, were obtained by recording: (a) the weight, before breakfast daily whenever possible, (b) the intake of fluid, and (c) the output of urine for the 24 hours (and any abnormal losses via the gastrointestinal tract). Weight change was corrected for caloric intake, especially at the stage when edema was occult. Clinical evidence of *true* dehydration was sought for, and fever, diaphoresis, hyperventilation, and high external temperature were noted as guides to the amount of *plain* water needed. Vomiting and diarrhea were noted; and signs of excessive electrolyte loss, especially after forced mercurial diuresis, were sought as guides to *salt and water* replacement.<sup>2, 7</sup>

*Laboratory Data.* In about half the observations the following data were obtained, often every few days: the hematocrit,\* the plasma or serum proteins (salting-out and falling-drop methods, usually simultaneously),† the plasma chlorides and the carbon dioxide combining power of the blood.‡ The daily albumin loss and chloride excretion in the urine,§ the maximum specific gravity of the urine,\*\* the venous pressure in centimeters of blood, and the vital capacity, were frequently determined.

The really vital data for this study, however, were clinical and obtainable at the bedside with *a scale and a graduate*, and by a careful *history and frequent examination* of the patient.

### MATERIAL

By the end of 1941, in a little over eight years, a wide variety of appropriate cases had been observed; all showed either marked gross edema or advanced cardiovascular disease. In table 1 the 402 cases and the 626 separate periods of treatment are classified according to the degree of edema present.

TABLE I

	With Gross Edema			No Gross Edema (Advanced Disease)	Totals on Régime
	Massive Anasarca	Marked Edema	Total Edema		
Cases.....	172	69	241	161	402
Periods.....	279	114	393	233	626
With Gross Heart Disease					
Cases.....	156	66	222	158	380
Periods.....	263	98	361	230	591

The 161 cases with "no gross edema" were studied because the degree of their cardiovascular disease and the complications present were such that one might expect a high fluid intake to produce edema or disaster.<sup>53, 54, 55, 56</sup> Of

\* WINTROBE, Jr. *Lab. and Clin. Med.*, 1932, xvii, 899.

† GREENBERG, Jr. *Biol. Chem.*, 1929, lxxxii, 545; and BARBOUR and HAMILTON, *Am. Jr. Physiol.*, 1924, lxix, 694.

‡ OSTERBERG and SCHMIDT, Jr. *Lab. and Clin. Med.*, 1927, xiii, 172-175. VAN SLYKE and CULLEN, Jr. *Biol. Chem.*, 1917, xxx, 289.

§ Esbach's and the modified Volhard-Harvey methods (KOLMER and BOERNER: "Improved Laboratory Technic," 1938, p. 107 and 162).

\*\* Determined while patient was dehydrated or by concentration tests.



these cases, 59 were admitted with an acute myocardial infarction; 22 had rheumatic heart disease with marked mitral stenosis; and most had pitting edema of the ankles on admission or lost from four to 12 pounds of occult edema during treatment. Approximately 50 per cent had had massive edema shortly before admission, or developed it shortly after dismissal after they had stopped the régime (figure 5 and table 5).

Of the 241 cases with "gross edema," the 69 cases placed in the "marked edema" classification showed signs of passive congestion or free fluid in *either* the chest or the abdomen, and deep pitting peripheral edema of the legs reaching well above the ankles.

In the "massive anasarca" group there are 172 cases of what earlier writers would call dropsy or "anasarca with ascites"; all showed clear signs of *both* hydrothorax and ascites in addition to extensive pitting or brawny peripheral edema reaching above the sacrum. This degree of edema was studied in 279 periods of observation, 70 per cent of the gross edema periods and 45 per cent of the entire series.\*

At the bottom of the table the cases with grossly evident cardiopathy, 90 to 95 per cent of all the material, are grouped according to their degree of edema. The material is further analyzed in the appendix.

#### GENERAL OBSERVATIONS

It soon became apparent that when sodium was properly regulated large amounts of water could be given with impunity and benefit to edematous patients and that the results with an actual forcing of fluids were better than those obtained by restricting fluids, whether the primary illness was nephritis, eclampsia, heart disease or some other disorder.†

The more severely ill patients who were sufficiently alert complained of extreme thirst, as has been noted by writers on dropsy since the sixteenth century, and showed marked clinical signs of "true" dehydration; their oliguria or anuria gave way to diuresis after their plain-water deficit was corrected, exactly as in dehydrated non-edematous patients (figure 1). Such patients sometimes showed the *loss of edema without loss of weight*<sup>98</sup> which is regarded as evidence of the presence of "thirsty" cells in a "brine-logged" body, and as due to a shift<sup>10, 11</sup> of the *water* of the edema fluid to dehydrated cells.‡

\* By the end of 1943 there were 364 periods of observation on 212 cases with "massive anasarca" out of 513 periods on 314 cases with "gross edema."

† Preliminary reports were read at the regional meetings of the American College of Physicians from 1936 on. Since the report in St. Paul in April 1942, these observations have been confirmed by competent observers elsewhere.<sup>99</sup>

‡ Both this phenomenon and the loss of weight without diuresis, so commonly seen, indicate that the restriction of fluids does not more often lead to disastrous dehydration because the body utilizes the *water* of the edema fluid that is released when edema is clearing and its sodium salts are passing out via the kidneys.

The distinction is rarely made between "true" dehydration which is a plain-water deficit resulting in cell dehydration and increased *concentration* of extracellular fluid, and so-called dehydration which is a *salt-plus water* deficit with loss of extracellular fluid volume.<sup>8, 10, 12, 14</sup>

The clearing of edema was *facilitated* by the forcing of fluids, for it was possible to reduce greatly the frequency of the use, and the amounts of, acid and mercurial diuretics; and the loss of edema was so rapid that oppressive degrees of hydrothorax or ascites rarely required aspiration (table 5). In certain instances it was noted that the very high intake was *essential* to the clearing of resistant edema (table 2) and to the restoration to useful activity of a significant number of cases that had been disabled by anasarca on restricted fluid régimes.

So-called "water intoxication" was not encountered although syndromes answering this description were seen which were found to be due to loss of body-fluid *volume* or disturbances of electrolyte pattern, or to "true" dehydration.<sup>18, 19, 30</sup> The correction of these extracellular fluid defects was most surely effected by giving a *proper* amount of salt and a generous *excess* of plain water, particularly when renal function was badly impaired; indicating that almost up to the point of cessation of cell function the kidneys remain effective and precise "guardians of the internal environment" so long as enough<sup>1, 3</sup> water reaches them (figures 4, 5, 7).

*Untoward Reactions.* There were none in this series when the intake was oral, even though intakes over 15 liters in 12 hours are recorded and one patient averaged 9 liters daily for 40 days; one dutiful hysteric drank two quarts of iced water in two hours, developed dilatation of the stomach, and was relieved promptly by lavage.

A sense of fullness and oppression was complained of about 20 times in the course of more than 2,000 intravenous isotonic supplements (table 7). It appeared sometimes after only 100 to 300 c.c. of solution had been given, especially in nervous patients or in those who later showed a characteristic pyrogenic reaction. The sensation as a rule passed off uneventfully with larger volumes being tolerated well later. In one case, after 700 c.c. (with mercupurin) a major convulsion occurred, yet six hours later 1,000 c.c. without mercupurin were tolerated and the next day 1,000 c.c. twice. However, the sensation is regarded, whatever its cause, as an indication for stopping a venoclysis promptly.

Acute pulmonary edema (table 5) developed during a venoclysis in three very ill patients, one recovering while the high intake was continued. The other two, who died within an hour, had received about 500 c.c. of isotonic solution (one with mercupurin). Both had been admitted in a near-terminal state with uremia, one in coma after a meningeal hemorrhage. Pulmonary edema and convulsions are not uncommon terminations in such cases\* on restricted fluid régimes and the usual supposition that the relatively small venoclyses precipitated the fatal episodes is not supported by certain observations.<sup>15, 16, 17, 20</sup>

*Immediate Effect of the Régime on Edema.* In the 393 periods of observation on cases with gross edema, the edema cleared entirely in 94 per cent, or 369 instances. In 17 of these periods, the patient was dying of some complicating condition such as subacute bacterial endocarditis, but died without recurrence of edema.

\* Withering's Case VI is pertinent: "a fair case for a trial of Digitalis . . . the third day after my visit she suddenly expired. I found she had not taken any of the medicine. Had she died under its use, is it not probable that the death would have been attributed to it?"<sup>48</sup>

In 24 instances, or 6 per cent, the régime failed and the patient died unrelieved of edema. These were all cases of advanced disease with the uremic syndrome present in most and with the oral intake negligible because of nausea, vomiting or semistupor. In 13 of these instances edema had been cleared completely in one or more earlier periods of treatment (see J. S., figure 6).

Obviously, in many of the 369 instances in which edema cleared completely, the result could be properly attributed, in whole or in part, to changes in such factors as the amount of rest, digitalis, oxygen, or diuretic drugs. But in the 103 instances shown in table 2, or 26 per cent of the 393 periods

TABLE II

Gross Edema Resisting Usual Therapy, Cleared by Change to the Régime  
103 control periods, with no other change

Cleared by Change: In Water and Salt and Diet Reaction .....	41
Cleared by Change: In Water only .....	22
(after incomplete In Sodium only .....	25
change régime) In Diet Reaction only .....	15
Recurrence of Edema from Opposite Changes: In Water, Sodium or Diet Reaction only .....	26

of treatment of gross edema, no change was made that might effect the clearing of edema *except to institute the high fluid régime*. In 41 instances the edema which had resisted a restricted fluid régime cleared promptly when the neutral diet and a high fluid intake were begun.

In the other 62 instances of clearing, shown in the next three lines, the individual importance of the three factors involved in this change is emphasized, for edema did not clear until a deficiency in one of the factors was corrected. In 22 instances edema did not clear, in spite of a proper sodium level and diet reaction, until the water intake was sharply increased, particularly when the concentrating power (maximum specific gravity) of the urine was especially low. In 25 instances clearing occurred only when an unappreciated source of sodium salts was cut off. In 15 instances edema resisted an adequate water intake and a proper level of sodium until the diet reaction which had been rendered basic by extra fruit and vegetables (in obesity or diabetes) was corrected.\*

The recurrence of edema was noted in the 26 additional instances shown in the last line as a result of a sharp decrease in water intake, or an increase in sodium ingestion, or a change to a diet yielding an excess of basic ash. In some patients massive edema returned when, led by some fad, they added to the "neutral" diet large amounts of basic ash in the form of carrot juice, orange juice or watermelon.

It was observed that marked edema cleared: (a) in classical myxedema with basal metabolic rates below minus 30 before thyroid extract was given,

\* Schroeder's observation that an intake of about 3,000 c.c. increased edema when the maximum specific gravity of the urine was low (1.016) was made with diets so low in sodium that their *net reaction was basic*.<sup>63</sup>

(b) in cases with deficient diets from habit or chronic illness before a diet adequate in protein or vitamin B was given, and (c) in pernicious anemia even when complicated by spinal cord changes, before the blood or general condition had improved. In the course of acute febrile illnesses edema developed with oliguria (from the *diversion of water to edema formation* by sodium retained from excess basic ash) on the customary liquid diets of salted soups, fruit juices and milk; both were corrected by a simple change to neutral or acid-ash liquids. Similar effects were observed in correcting edema or oliguria by substituting calcium carbonate for *sodium* bicarbonate in ulcer cases,<sup>19</sup> acetyl salicylic acid for *sodium* salicylate in severe rheumatic fever, and vitamin concentrates for large amounts of orange and tomato juice in surgical cases.

Some patients with very mild cardiac disease but *marked* edema whose histories showed that they had been on diets high in basic ash or salted foods, cleared 15 or 20 pounds of edema without the use of digitalis or even acid drugs. Without the history, such patients might have been classified as examples of marked congestive heart failure with "cardiac edema" cleared by "spontaneous" diuresis, whereas others without clinically apparent cardiovascular or renal disease might be thought to have developed "idiopathic" edema.

In all very ill non-edematous patients, too, the régime with its regulation of sodium proved useful in the prevention and correction of dehydration and anuria. Thus a comatose patient with sulfonamide crystallization and an anuria of 42 hours' duration responded to 16 liters of water in 36 hours.

Such observations suggest that diet reaction and salt play a more important rôle than thyroid, vitamin, or protein deficiencies or than even moderate degrees of myocardial or renal insufficiency, in the development and clearing of edema; and that a proper *regulation* of sodium is quite as important as a proper water-balance to the correction and avoidance not only of edema but of dehydration and oliguria or anuria; and there are obviously other, more far-reaching, implications of these observations.\*

*Late Effect of the Régime on the Control of Edema.* The immediate relief of edema in the hospital, even of edema that has resisted other régimes, is not as severe a test of a régime as its ability to control edema out of the hospital, while permitting greater activity, without shortening life.

Thirty-nine cases, 14 with rheumatic chronic valvular disease and 25 with degenerative heart disease, or 22 per cent of the 172 cases with massive anasarca, had been disabled by their anasarca and were unable to engage

\* Implications such as that: the Starling hypothesis and the diagnostic and therapeutic significance of congestive heart failure require reevaluation. The rôle of excess salt and basic ash in the impoverished diets of nutritional or war edema should be studied. The indications for a high protein diet require modification. Salt replacement in hot environments with edema may be due to cellular dehydration. Many serious phenomena associated with edema should cease.<sup>5, 25, 40</sup> Throughout this paper a clear distinction is attempted between the *facts* observed and what they appear to *suggest or imply* for as Beaumont says, "facts are more persuasive than argument, however ingeniously made."

in any useful activity for from one to nine years in spite of adequate treatment by the usual methods. On the high fluid régime their anasarca cleared and was so well controlled that they resumed nearly normal activity and were economically useful again for periods of from one to eight years. The gravity of their primary disease is indicated by the fact that 16 of the 39 died after from one to eight useful years, only 6 of the 16 suffering a recurrence of edema a short time before death. No greater objections to the continued use of the régime on the part of these patients were encountered than are met in any series of patients who are subjected to dietary regulation<sup>69</sup> (figures 3, 5, 8).

*The Mortality Statistics* from this series will be fully reported later but up to October 1944 they appear to support those observations that indicate that the long range results are more satisfactory than those obtained on restricted fluid régimes. Prognosis for life after the onset of congestive heart failure is notoriously poor; thus, in Dry's report<sup>50</sup> of a series of 150 cases treated by accepted methods with restriction of fluids, 40 were living after 5 years, a survival rate of 27 per cent. Of the cases with gross edema in this series, there are 156 cases with advanced heart disease as their *primary* disease who survived the initial admission and all but two have been traced. Of the 154 cases whose status is known, 102 were started on the high fluid régime more than five years ago and 40 of them are living after five years, a survival rate of 39 per cent. The comparison in favor of the high fluid régime seems more than fair since 74 cases, or 72 per cent of the 102 cases, showed the degree of edema described above under "massive anasarca" when they were first seen five years ago, and in 22 of the 102 cases, or 21 per cent, the onset of their congestive failure preceded their start on the high fluid régime by an average of 6.3 (2 to 15) years.

#### SPECIFIC OBSERVATIONS AND COMMENTS

The data shown are from cases with severe advanced disease, marked resistant edema, and complications that might be expected to respond disastrously to a high fluid intake. Such cases were selected for presentation because mild disease and its edema often respond to such simple measures as rest, and quite often in spite of, rather than because of, some more imposing therapy. The diagnoses and the advanced degrees of disease of the cases in the last four figures were verified at a well known medical center.

Figure 1. The Universal Response of Oliguria to Water and of All Forms of Edema to the High Fluid Régime: This figure offers a comparison of the data commonly obtained during the first few days of treatment of patients, both with and without edema, who are suffering from a lack of plain water. In the six cases there is the same early discrepancy between water intake and urine output. The first two cases were not edematous and are from Coller and Maddock's early work.<sup>6</sup> The next four had developed massive edema in the course of four different primary illnesses;

they were seen early in this study and received no acid or mercurial diuretics to produce a forced diuresis.

J. N., male, age 26 (Coller): A normal young adult, after four days experimental deprivation of plain water, developed oliguria, nitrogen retention, abnormal urinary findings, increased specific gravity of the blood and a loss of 6 per cent of his body weight in spite of an adequate caloric intake. The data are taken from the first days after he was permitted to drink again; in the first day he drank over 6,000 c.c.\* of

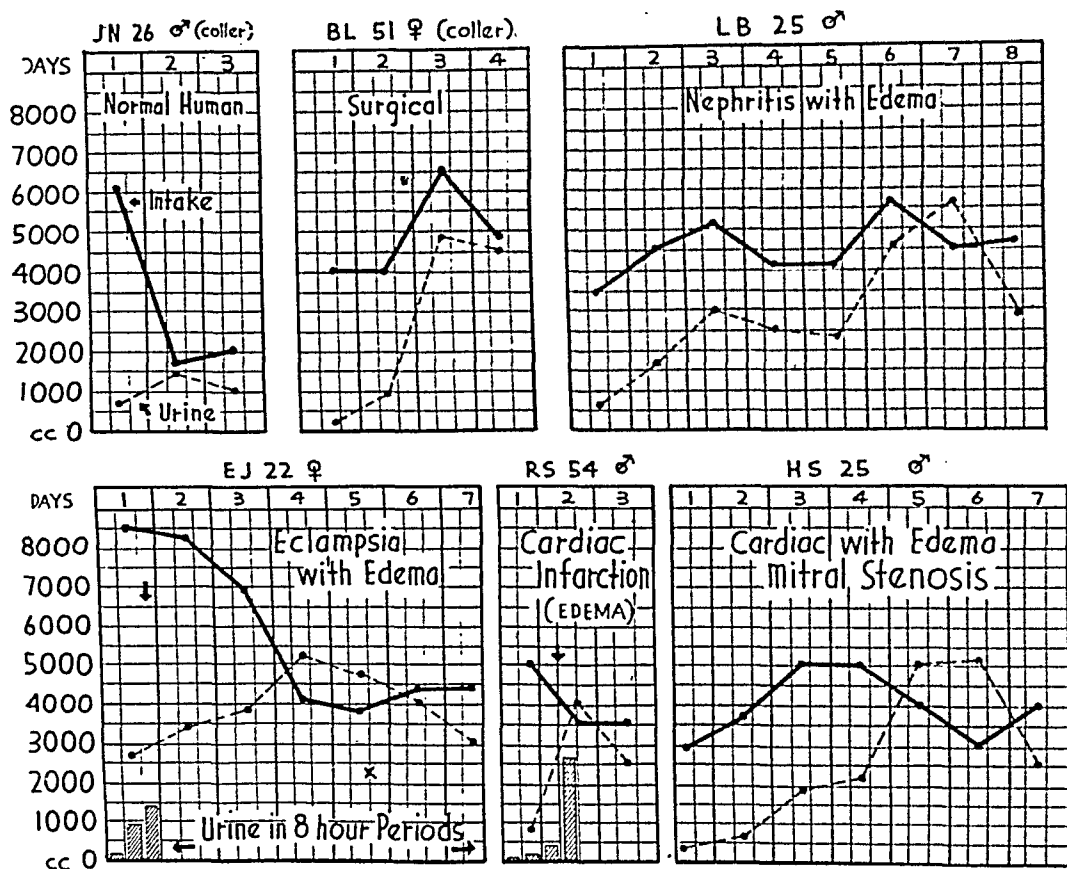


FIG. 1. The universal response of oliguria to water and of all forms of edema to the high fluid régime.

water, of which less than 600 c.c. reached the kidneys. The second day, diuresis occurred with correction of the azotemia and the 9 gram salt retention; and not until the third day was the normal relationship between intake and output, as shown in an earlier control period, reestablished.

B. L., female, age 51 (Coller): A typical example of the correction of a water deficit anuria in a seriously ill, non-edematous surgical patient; she had lost one

\* Certain obvious abbreviations are used: c.c. stands for cubic centimeters of water or solution; cm. after the venous pressure readings, stands for centimeters of blood; mg. is used for milligrams per 100 cubic centimeters;  $CO_2CP$  followed by the reading, stands for the carbon dioxide combining power of the blood, and volumes per cent; grams after serum protein, is used for grams per cent of total serum protein, and the number given in parenthesis is the number of grams per cent of the serum albumin fraction. The figures after blood pressure refer to systolic and diastolic pressures measured in millimeters of mercury.

kidney years before. Her azotemia was marked. The degree of true dehydration was such that 8,000 c.c. of water in the first 48 hours did not adequately correct the water deficit as indicated by the fact that less than 1,000 c.c. of water reached the kidney during the second day. However, on the third day, during which the intake was 6,500 c.c., the oliguria was overcome, and nearly 5,000 c.c. of urine were elaborated by the single kidney.

*Case 216.* L. B., clerk, age 25 in 1935, was admitted with post-infectious sub-acute glomerulonephritis because of swelling of the abdomen, which had increased during the preceding three weeks in spite of a low intake and purging. There was pitting edema of the abdominal wall and extremities, and edema of the face. The liver was palpable, ascites was present, and dullness and coarse râles were present at the right lung base. The albuminuria was such that the urine solidified on boiling. In 10 days on an average daily intake of over 4,500 c.c., with intravenous supplements for five days, all signs of edema and ascites cleared with a weight loss of 20 pounds and a drop in blood urea from 64 to 16 mg. During the first day there was perceptible increase in edema, yet by the end of the second day, while the urine output was still about 6,000 c.c. below the intake for the two days, there was marked clinical improvement. The only clinical residuals in 1943 are a slight cardiac enlargement and the low fixed specific gravity of the urine of 1.015.

*Case 229.* E. J., ranch housewife, age 22 in 1935, was admitted in coma on March 13 at 2 a.m. in the eighth month of her pregnancy. Ten major convulsions had occurred in the eighteen hours prior to admission; it was known that she had not voided for 25 hours, and catheterization yielded only 60 c.c. of urine which solidified on boiling. The blood pressure was 180 mm. Hg systolic and 100 mm. diastolic. Gross generalized edema was present; the face was blotchy and cyanotic, the breathing stertorous and the tongue badly injured. The fundi showed diffuse retinal edema with small retinal hemorrhages on the right.

Convulsions were controlled with sodium phenobarbital. Operative intervention did not appear advisable and the high fluid régime was tried on the basis that the convulsions and coma, as well as the anuria, might respond to the correction of a severe plain-water deficit and relief of cellular dehydration.\*

During the first eight hours 4,000 c.c. of isotonic dextrose were given, 2,000 c.c. by vein and 2,000 c.c. subcutaneously and only 175 c.c. of urine were obtained by catheter. By 4 p.m. 14 hrs. after admission, when 6,000 c.c. had been received parenterally and only 1,000 c.c. of urine had been obtained, she roused and asked for water. In spite of a perceptible increase in edema her clinical improvement continued, no convulsions occurred, and she drank 1,000 c.c. of water by midnight with little urging. She received over 8,000 c.c. of water daily, for the first two days (the arrow indicates the time of the first definite clinical improvement, interpreted as due to the correction of her water deficit). Edema began to clear on the third day, disappeared rapidly from the fourth day on when diuresis began, and was no longer detectable by the end of the sixth day with the average daily intake at 6,000 c.c. Labor, induced on the fifth day, resulted in a stillbirth, although fetal heart sounds were present until

\* During 1934 some edematous, non-pregnant patients admitted with major convulsions had responded well to the régime; epileptic convulsions seemed better controlled; convulsions in acutely ill children responded well to swift rehydration (a 22 kilogram child received a liter of isotonic dextrose by vein, aroused in three hours thirsty, and drank 3.5 liters of water in the next ten hours); and brain injury cases were managed for weeks with from 3 to 5 liters of isotonic solution daily by vein, with recovery.

Such results suggested that brain cell injury from the effects of cellular dehydration might actually be an important factor in the production of convulsions. This hypothesis, which an associate<sup>58, 59</sup> has described, is at least no more inadequate than the "edema of the brain" hypothesis which has led to the practice of restriction of fluids and the use of strong hypertonic solutions.

the second stage. With careful supervision on the high fluid régime she bore living children uneventfully in 1937 and 1939. In 1944 vascular injury is still occult.

A similar case, W. L., age 24, was seen recently; both mother and child survived. The intake was 5,000 c.c. the first day and 9,200 c.c. on the second day when her clinical improvement began in spite of perceptible increase in edema. The urine output the first day was 900 c.c. and diuresis and the clearing of edema did not begin until the third day; the average daily urine output continued at 7,500 c.c. for three days. On the second and fifth days there was no laboratory evidence of any disturbance in the composition, concentration, or volume of the blood.

Case 90. R. S., rancher, aged 54 in 1934, was admitted for repeated, violent Adams-Stokes convulsions which ceased when 5,000 c.c. of water had been received and less than 800 c.c. of urine had been elaborated (see figure 2 for the typical hourly urine output of such re-hydration periods). He recovered from shock and the convulsions ceased, as indicated by the arrow, before diuresis began and in spite of the same perceptible increase in his massive generalized edema noted in the case above. Edema cleared by the end of the sixth day on an average daily intake of 3,800 c.c.

Case 169. H. S., male, clerk, age 25 in 1935, was admitted with massive edema of the lower extremities, moderate bilateral hydrothorax, and ascites of two months'

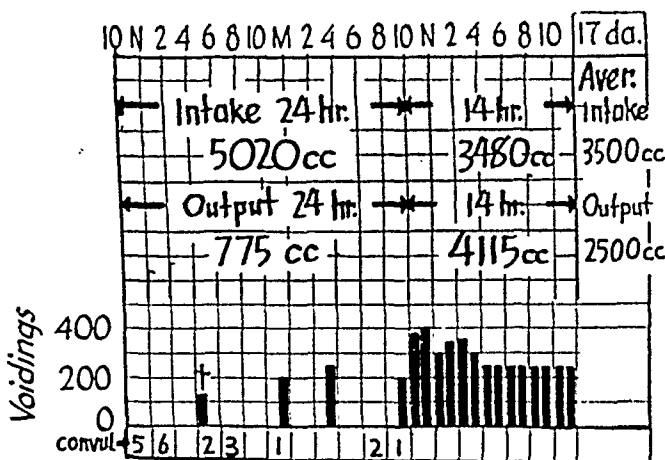


FIG. 2. R. S., No. 90. Acute myocardial infarction.

duration. There was a history of rheumatic fever, the heart was much enlarged, and mitral stenosis and auricular fibrillation were present. After 16 cat units of digitalis in the first 24 hours the apex rate dropped from 170 to 80 per minute, the pulse deficit disappeared and there was considerable symptomatic relief. In spite of these digitalis effects the oliguria persisted for two days and there was no diuresis until the fifth day, although there was continued marked general improvement. After diuresis began edema cleared completely by the seventh day with a weight loss of 17 pounds, on an average daily intake of 4,600 c.c. The blood urea dropped from 60 to 30 mg. He tolerated light work and a high fluid régime with no recurrence of edema until he died in 1937, from subacute bacterial (*Streptococcus viridans*) endocarditis.

Comment. These cases emphasize that true dehydration exists in the more seriously ill edematous patients since the correction of their oliguria follows the same pattern as in dehydrated non-edematous patients.<sup>6, 8</sup> The response of such patients to a high fluid intake suggests also that many of the phenomena which we attribute to edema may in fact be due to cellular



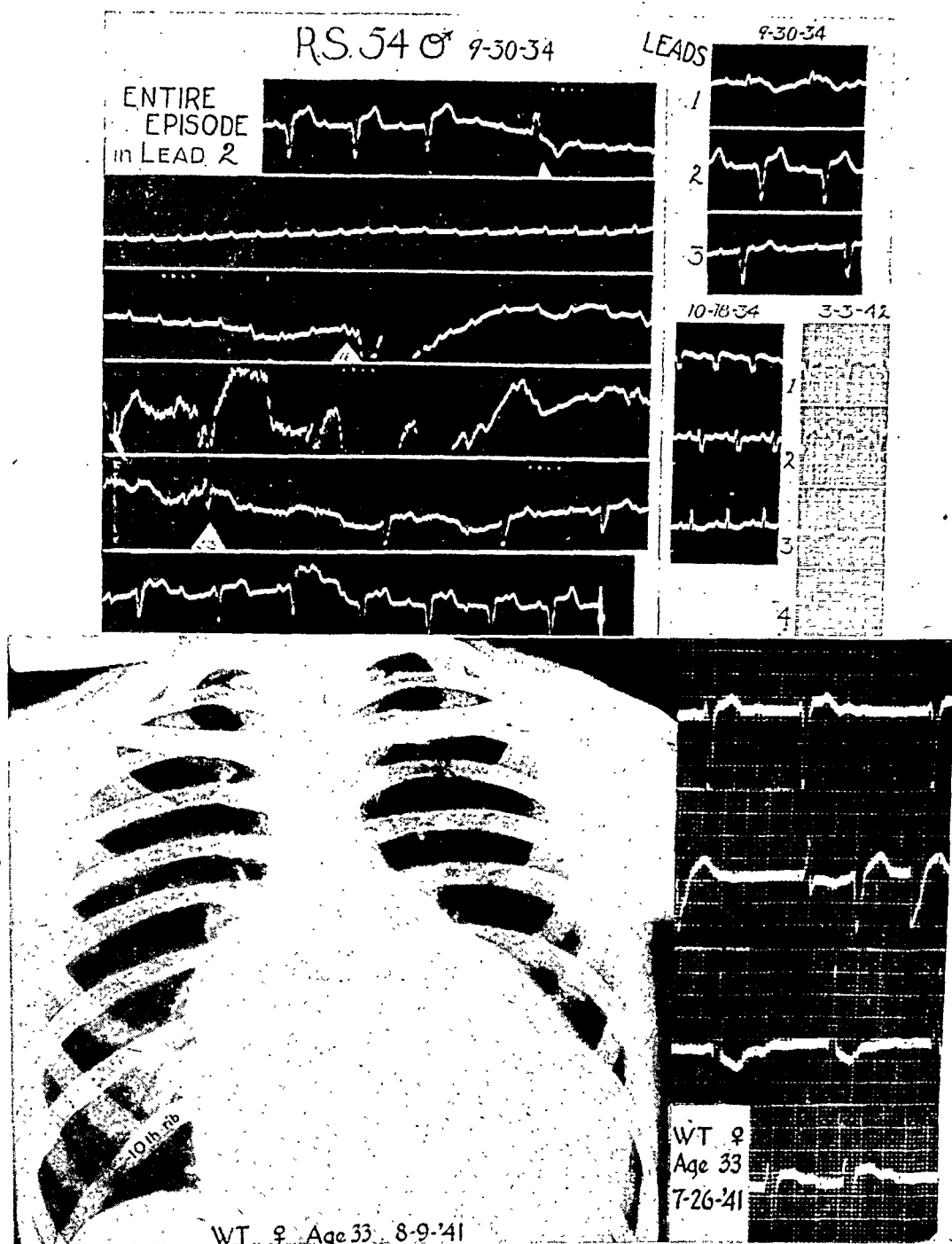


FIG. 2A (Above). The first tracing from Case 90, figure 2, covers an entire Adams-Stokes convulsion and shows, as the white wedges indicate, a duration of ventricular standstill of 33 seconds, the convulsion beginning at 16 seconds. The standard leads on that day, 9/30/34, show changes compatible with an acute myocardial infarction, and the complete A-V dissociation which disappeared within 36 hours. The tracings of 10/18/34 show an atypical right bundle branch block and other changes which persist, with slight alteration, in the 3/3/42 record seven and one-half years later.

FIG. 3A (Below). The roentgenogram of the chest and the electrocardiogram from Case 155, figure 3 are representative of many obtained from the 70 cases of rheumatic valvular disease in this series.

The 8/9/41 film was taken standing in full inspiration at 6 feet after the loss of 50

dehydration, for the same symptoms and signs may be relieved in the edematous and non-edematous alike by the correction of a plain-water deficit; and the clinical improvement in the edematous often precedes diuresis and is not hindered by transient increase of the generalized edema. Finally, the response of the four edematous cases to the high fluid régime indicates that the volume increase of interstitial fluid which we call edema responds to the same therapy in the same way regardless of what primary disease is present.\*

Figure 2. Acute Myocardial Infarction: The high fluid intake seemed very effective in overcoming the oliguria, shock and azotemia which were encountered in about half of the 114 cases of acute myocardial infarction; 55 of these cases, like the case shown in this figure, had marked edema. In this case major convulsions from ventricular standstill, and an anuria of 20 hours' duration, were relieved. (See his figure 1 data.)

*Case 90.* R. S., rancher, age 54 in 1934, had had increasing shortness of breath on exertion for several years. He was admitted, six days after a typical acute coronary occlusion, in shock with a blood pressure of 90 mm. Hg systolic and 50 mm. diastolic, and with basal râles, a tender palpable liver, and generalized edema. He had not voided during the preceding 14 hours, and the 125 c.c. of urine obtained by catheter, six hours after admission solidified on boiling. Severe Adams-Stokes convulsions were occurring, four before and 11 in the first four hours after admission. The ventricular rate between standstills was about 40 per minute (figure 2A). Because he failed, in spite of oxygen and adrenalin and because of the signs of congestive failure present, he received 8 cat units of digitalis in the first six hours, in addition to two 500 c.c. intravenous supplements of dextrose after the first four hours, and all the water he could take orally between his attacks. (The black columns represent the hourly voidings in the two hour periods into which his first 38 hours are divided; the voidings of the last eight hours totaled 1,920 c.c. and are averaged at 240 c.c. per hour.)

The first specimen of 125 c.c., obtained six hours after admission, was all the urine elaborated in 20 hours; in the next seven hours only 200 c.c. were obtained, and in the last 11 hours of the first 24, only 450 c.c. The convulsions, as shown at the bottom of the figure, occurred in lessening frequency as rehydration proceeded and ceased by the end of the 24 hours when the intake had reached 5,020 c.c. and the output of urine was only 775 c.c. During this period of clinical improvement there was perceptible increase in the edema and the rate of urine excretion remained low, about 20 c.c. per hour the first half, and 40 c.c. per hour in the last half of the 24 hours, in contrast to the rate of 300 c.c. per hour during the 14 hours of diuresis that followed. About six hours after diuresis began, the complete heart block disappeared

\* See also cases 226-239, tables 3 and 6. In some instances, even the ascites of carcinomatosis, and the hard, tight edema of deep femoral vein thrombosis cleared rapidly after the régime was begun; which recalls Starling's remark on experimental edema of the tongue: "One can, however, produce a very fine oedema . . . by the injection of a large amount of normal saline into the circulation." <sup>9, 95, 60</sup>

pounds of anasarca and ascites, to avoid exaggeration of heart size by any elevation of the diaphragm; a film one month later was identical.

The electrocardiogram is characteristic, with auricular fibrillation and changes compatible with marked right ventricular preponderance and/or right bundle branch block; chest lead is IV F. (See tracing in figure 5 for other characteristic changes.)

with a rise in the ventricular rate from 40 to 80 in the next four hours. With diuresis the edema cleared rapidly and convalescence was uneventful during the next 17 days while his intake averaged 3,500 c.c. daily. The blood urea dropped from 75 to 23 mg. by the fifth day. He continued moderately active through 1943 and controlled edema by periodic returns to the high fluid régime.

A similar case (92), E. P., male, age 50 in 1941, was admitted five days after a posterior infarction, in extreme shock with the blood urea at 196 mg. Anuria persisted for 42 hours until 10 liters of water had been received. Much of the average daily intake of 5,000 c.c. of water was dissipated by fever and diaphoresis and the edema and oliguria persisted until the fourteenth day, after which diuresis began and the clearing of edema and azotemia was rapid. Isotonic intravenous supplements totaling 3,000 c.c. daily were tolerated during the 14 most critical days.

Another case (89), J. A., male, age 62, with mitral stenosis and aortic regurgitation, was admitted with massive edema two weeks after a posterior infarction. The edema cleared with a 20 pound loss of weight in eight days on an average daily intake of 4,000 c.c. The clinical diagnosis was confirmed at autopsy following an acute anterior infarction a year later.\*

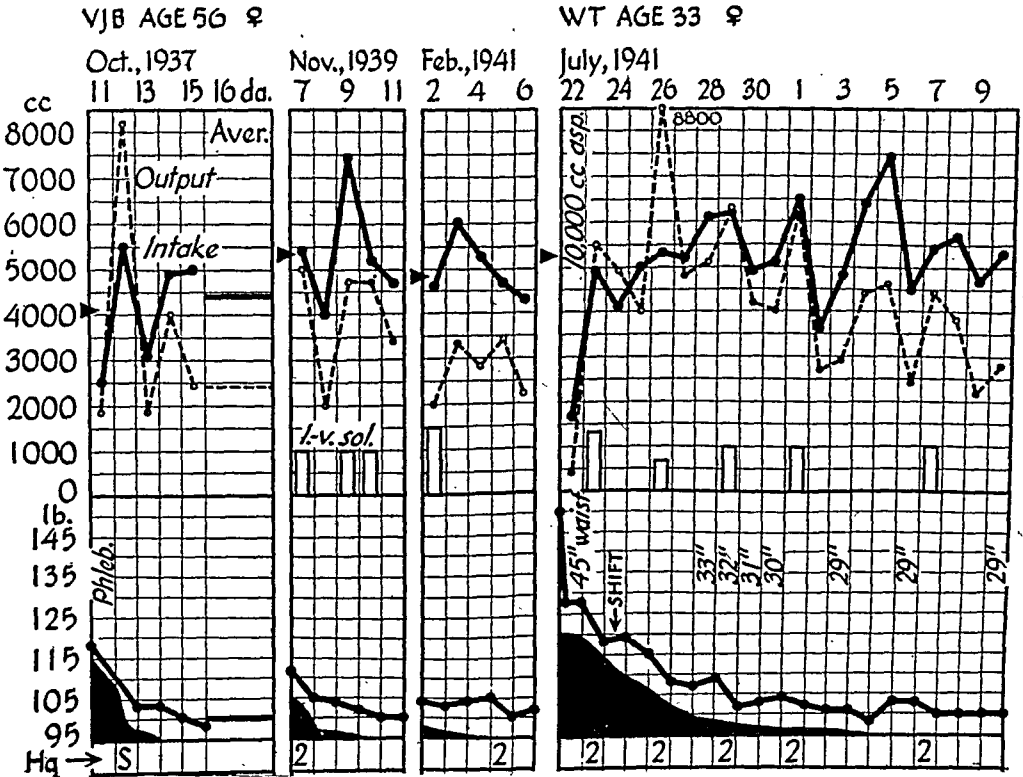


FIG. 3. Chronic valvular heart disease.

*Comment.* Such cases indicate that a badly and recently injured myocardium tolerates a high fluid intake well with the correction of shock, oliguria and azotemia, and with the clearing of edema when it is present.

Figure 3. Chronic Valvular Heart Disease: In the entire series there

\* Courtesy Dr. J. M. Askey.

were more than 60 cases with marked narrowing of the mitral valve (25 of these with aortic insufficiency) as a result of rheumatic endocarditis, the diagnoses of which were based on the presence of characteristic diastolic murmurs. Most of the 73 instances of auricular fibrillation were found in these cases. Both of the cases in figure 3 had auricular fibrillation and aortic regurgitation in addition to mitral stenosis. The first case also had hypertension of a magnitude of 230 mm. Hg systolic and 120 mm. diastolic. The size of the fluid intakes recorded in the two cases is the more striking because their edema free body-weight was less than 100 pounds (45 kg.).

(In the upper tier of the figure, the *heavy black line* shows intake for the day; the *black wedge* indicates the average daily intake for the period; the *plain columns* represent the total volume of isotonic solution given by vein during the day; the *light broken line* shows the daily output of urine. In the lower tier the *heavy black line* represents weight and the *solid block* indicates the degree of edema present. At the bottom of the figure the use of a mercurial diuretic is indicated by the letter S for a suppository, or the number 2 for 2 c.c. of diuretic given by vein.\*)

*Case 159 (Left).* V. J. B., housewife, age 56 in 1937. Her history included scarlet fever and three attacks of rheumatic fever between the ages of six and 14, four pregnancies carried with difficulty between the ages of 22 and 27; and hospitalization at the age of 47 with the onset of auricular fibrillation in October 1928, for her first severe break in compensation. From that time she remained economically useless because of recurrent anasarca in spite of long periods of rest in bed at home, 14 hospitalizations, and adequate and accepted treatment by a competent internist. During these nine years she was digitalized and received intravenous mercurial diuretics, acid drugs and a low salt diet, and several phlebotomies were done because of attacks of left ventricular failure. From 1934 on the blood pressure rose; in 1937 it ranged from 210 mm. Hg systolic and 100 mm. diastolic to 230 mm. systolic and 120 mm. diastolic; albuminuria was always present during her worst breaks. In the year preceding the first admission shown here, distress was continuous in spite of four hospitalizations and many weeks in bed at home.

In the *October 1937 admission*, pitting edema reached to the scapulae posteriorly, right hydrothorax and moderate ascites were present, and the liver pulsated and its edge was palpable at the level of the umbilicus in the mid-line. Extreme dyspnea, orthopnea and cyanosis were present and with the patient in a sitting position, the neck veins were much distended.

The only changes made in her previous régime were to increase her fluid intake and place her on a neutral diet. A 200 c.c. phlebotomy was done on the first day. A mercurin suppository, given on the second day, resulted in a tremendous diuresis even though mercupurin by vein had been previously ineffective. She tolerated an intake of 5,500 c.c. on the second day and a daily average of 4,200 c.c. for the five days, during which her weight dropped 20 pounds and all detectable signs of edema disappeared. There was no recurrence of edema during the next 16 days, the weight remaining at 100 pounds on an average daily intake of 4,200 c.c. The liver decreased greatly in size and orthopnea disappeared for the first time in 18 months.

\* Mercurial diuretics were not observed to produce any evidence of renal injury when the water intake was adequate, even in nephritis. They were used to assist in clearing edema in only the more resistant or more distressed cases, and occasionally to test for the presence of occult edema.<sup>61</sup>

She followed her régime faithfully at home, taking a measured 3,000 to 4,000 c.c. of water daily. She resumed her housework and some social activities for the first time in nine years. In the past seven years she has been too active and minor lapses in the régime have resulted in the development of perceptible edema which she has controlled at home by resumption of the régime, without mercurial diuretics. She has been hospitalized only four times since 1937, for periods of from five to seven days. The *November 1939 admission* was precipitated by a digestive disturbance which put her off her régime; she cleared 10 pounds of edema in four days on an average daily intake of 5,400 c.c. with three intravenous supplements of 1,000 c.c. On the third day she tolerated 7,500 c.c. in 24 hours. The *February 1941 admission* was for an acute respiratory infection; she cleared a few pounds of occult edema on an average daily intake of approximately 5,000 c.c. There have been two other similar admissions through 1943.

*Case 155 (Right).* W. T., ranch housewife, age 33 in 1941 (figure 3 A), had severe rheumatic fever in March 1940 during her fifth pregnancy, which was terminated successfully in December 1940, but was followed by increasing weakness and shortness of breath. She was hospitalized from February 9 to June 15, 1941, during which time anasarca appeared and increased in spite of digitalis, the restriction of fluids, and transient response to mercurial diuretics; during a month of strict bed rest at home, prior to admission, her symptoms and the size of her abdomen increased steadily.

On admission on July 22, 1941, at noon, extreme orthopnea, dyspnea and intense cyanosis were present. The signs of hydrothorax extended to the mid-scapula on the right and covered the lower one-third of the lung field on the left. The abdomen was greatly distended and the enlarged liver was ballottable through the ascitic fluid. Pitting edema extended to the mid-scapulae and was present over the lateral abdominal walls, and the edema of the thighs and legs was tight and brawny. Ten liters of ascitic fluid were permitted to flow through a small trocar over a period of 90 minutes with the resultant loss of 22 pounds of weight, but with only moderate relief of her extreme dyspnea and orthopnea and much ascitic fluid remained after the aspiration. The neck veins remained distended when the patient was sitting, and the venous pressure, four hours after aspiration, was 23 cm. of blood (25 cm. with liver pressure). There was no spontaneous diuresis following the aspiration. She was permitted to rest the balance of that day.

The régime was started the second day. There had been no change in the peripheral edema or the level of hydrothorax overnight, and she still complained of intense thirst, as she had on admission. On this first day of the régime, with the venous pressure unchanged, she tolerated 1,300 c.c. by vein with a total intake of 5,000 c.c. and lost 10 pounds of weight. In the next 24 hours there was no further weight loss, although there continued to be a further marked loss in edema, indicating a shift of water to the cells during that time. By the fourth day the venous pressure had dropped to 7.5 cm. of blood. By the end of the twelfth day of the régime, on an average intake of 5,500 c.c. daily, she had lost all evidence of peripheral edema, ascites, and hydrothorax with a loss of 28 pounds of weight (in addition to the 22 pounds removed mechanically on the day of admission).

At the level of the umbilicus the abdomen measured 45 inches on admission, 30 inches on the eighth day, and 29 inches at the time of discharge, although the actual caloric intake during her last 10 days exceeded 3,000 calories daily. After dismissal she gained 18 pounds of true body weight by October 10, on which date the circumference of the abdomen was only 28½ inches.

This 45 kilogram (100 lb.) woman (whose total blood volume was about 4,000 c.c. and whose normal interstitial fluid volume<sup>12</sup> was about 7,000 c.c.) was relieved of about 23 kilograms of excess extracellular fluid, while the average daily water intake

was 5,500 c.c., with a maximum in one day of 7,500 c.c., and while there was an average daily output of urine water, in the first five days, of 5,600 c.c., with a maximum on the fourth day of 8,800 c.c. Yet, from the first to the sixth day, the plasma chlorides rose from 511 to 594 mg. and the  $\text{CO}_2\text{CP}$  changed only from 66 to 67; and in another 12 days with the average daily urine output at 4,300 c.c. the chlorides dropped only to 577 mg. and the  $\text{CO}_2\text{CP}$  to 61. On the same days (2nd, 6th, and 18th) with the diet protein at 70 grams, the serum proteins were 6.0 (3.2), 5.4 (3.0) and 5.2 (2.9) grams and the hematocrit readings were 44, 53, and 51 per cent.

General improvement continued during August, with bed rest at home. The régime was well followed and there was no recurrence of edema. By October she had resumed full care of her ranch home and five children. On October 10 and December 12, 1941, after a 200 mile drive from her home she showed no evidence of even peripheral edema; she was taking a *measured* 4 liters of water daily. She continued active and edema free until her sudden (embolic) death in February 1942.

A similar case (156), B.P., male, age 28 in 1939, whose roentgenograms and electrocardiograms were like those of W. T's, died in uremia in March 1942. Autopsy showed multiple, large, fresh pulmonary infarctions and a mitral orifice narrowed to a slit that just admitted loosely the handle of a scalpel. In May 1941 he tolerated for 21 days an average daily intake of 6,000 c.c., including 2,000 to 3,000 c.c. by vein daily the first eight days, and cleared his edema completely with a weight loss of 25 pounds.

*Comment.* Such cases as these show that hearts handicapped by obstructed and incompetent valves and auricular fibrillation tolerate the high fluid régime even in the face of high venous pressures,<sup>34</sup> arterial hypertension, and myocardial damage. In cases like V. J. B. the difference between the nine years of disability and the seven years of useful activity appears to lie in the difference between the restricted fluid régime and the high fluid régime (see also A. V. F., figure 5). The cardiac veterans who have followed both régimes faithfully, have generally found the high fluid régime the lesser of two evils and more effective in controlling their edema.

The data from W. T. indicate also how well the handicapped kidneys<sup>30, 31, 64</sup> of severe congestive heart failure regulate the concentration and electrolyte pattern of the extracellular fluid while permitting great losses of excess interstitial fluid, in spite of the daily ingestion of volumes of water and the daily loss of volumes of urine water that actually exceed the blood volume and approach the normal volume of the interstitial fluid. There was no evidence here of the production of so-called "water intoxication" or of the "washing out" of *needed* sodium or chloride.

Figure 4. Resistant Massive Anasarca in Advanced Cardiovascular Disease: Withering comments: "If the belly be tense, hard . . . or the limbs in anasarca solid and resisting, we have but little to hope." Both the cases in this figure had massive anasarca of many months' duration, neglected or resistant, with the tight, hard swelling of brawny edema reaching well up the trunk, bilateral hydrothorax reaching to the mid-scapulae, and ascites with tight swelling of the abdomen and brawny edema of the abdominal wall. Both cases showed a high grade of arteriosclerosis and hypertension, and the second case, for good measure, had mitral stenosis and myelogenous leu-

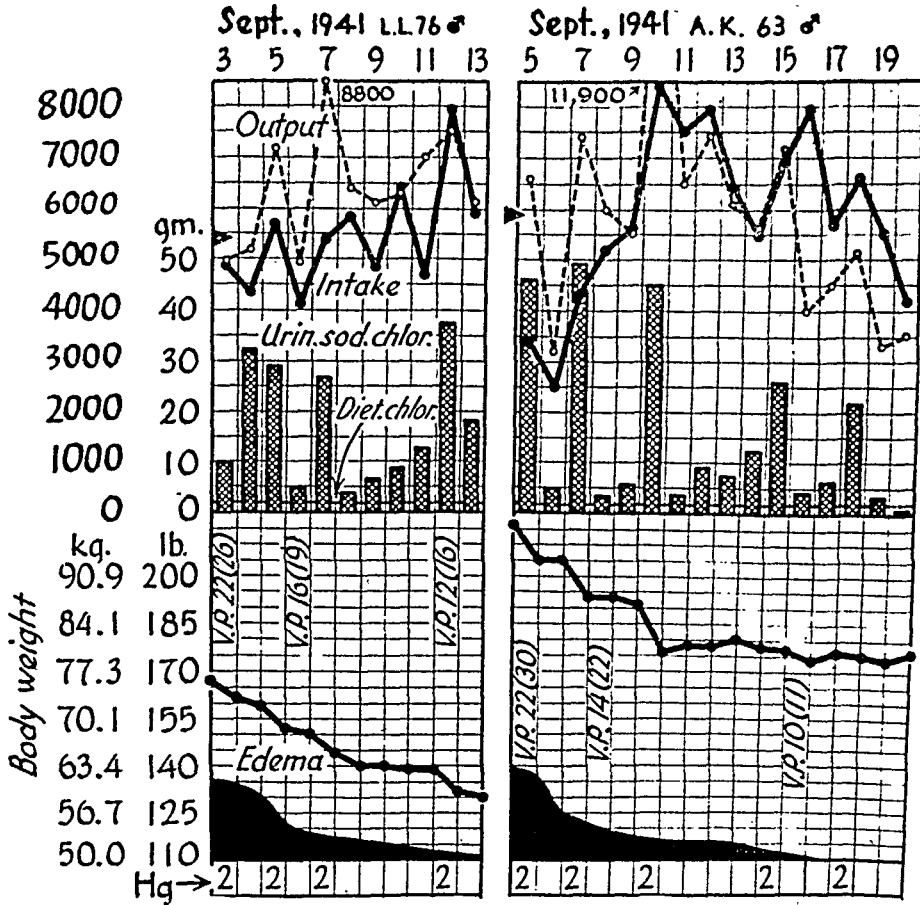


FIG. 4. Resistant massive anasarca in advanced cardiovascular disease.

kemia. The first patient complained bitterly of thirst on admission and both patients showed a maximum specific gravity of the urine of 1.016 or less.

*Case 1 (left).* L. L., male, retired, age 76 in 1941, had had cardiac symptoms for 14 years; a blood pressure of 200 mm. Hg systolic and 120 mm. diastolic in 1927; angina of effort since July 1931; increasing dyspnea and edema since 1937; and there had been massive swelling of the legs and abdomen for four months prior to admission. The examination showed the extent and kind of anasarca, with ascites and hydrothorax, described above.

His thirst was still intense after 2,000 c.c. of water (as isotonic dextrose) by vein and 1,500 c.c. of water taken eagerly by mouth. He lost 37 pounds of edema in 10 days with an average daily intake of 5,500 c.c. Most of the edema cleared in the first six days, but there was a perceptible loss of edema in the next three days without further loss of weight,<sup>68</sup> indicating the shift of water to thirsty cells (which had been kept dehydrated by the forced mercurial diuresis). On the tenth day an intake of 8,500 c.c. did not prevent a weight loss of nearly 10 pounds. In his first 12 hours he tolerated 1,000 c.c. of isotonic dextrose by vein while the venous pressure was 22 cm. (26 cm. with liver pressure), and the pressure fell in the usual manner as the edema cleared,<sup>70</sup> to 16 cm. in three days and to 10.5 cm. on the tenth day.

The urinary sodium chloride excretion for 24 hours, in grams, derived in the usual manner from the actual urine chloride, is shown in the cross-hatched columns.

(Ingested chloride daily was derived from 4 grams of ammonium chloride and about 2 grams of diet sodium chloride.) There is no real parallel between the amount of urine chloride and the volume of urine water, even when a mercurial diuretic forced the kidneys, for, expressed as sodium chloride, on the second day 35 grams appear in 5.0 liters, but on the fifth day, 27 grams appear in 8.8 liters, or only half as much salt per liter of water, and on the fourth and sixth days less than 5 grams appear in 5.0 and 6.5 liters. The kidneys apparently permitted the passage of sodium and chloride or water in proportions that protected the concentration and electrolyte pattern of the internal environment; thus, in 11 days the plasma chlorides ranged from 544 to 552 mg., the  $\text{CO}_2\text{CP}$  from 62 to 54, and the plasma proteins changed from 6.1 (3.9) to 4.9 (2.9) grams in a direction opposite to the hematocrit which rose from 36 to 45 per cent. He resumed moderate activity by the middle of October, and on the régime there was no recurrence of edema throughout November and December. He died in January with uremia following an acute myocardial infarction.

*Case 157* (right). A. K., male, rancher, age 63 in 1941, had had dyspnea on exertion since rheumatic fever at age 24. He had been digitalized and intermittently disabled because of edema and orthopnea since 1936, and during the year before admission there was increasing resistant anasarca and the appearance of large cervical lymph nodes. Examination: The cervical and axillary lymph nodes were enlarged and the blood smears were diagnostic of chronic myelogenous leukemia. The spleen and liver were greatly enlarged, as was the heart, which showed the presystolic murmur of mitral stenosis. The maximum specific gravity of the urine was 1.016, and the blood pressure was 170 mm. Hg systolic and 110 mm. diastolic. His degree of anasarca was that described above. He lost 40 pounds of weight in six days on an average daily intake of 6,000 c.c. The maximum intake of 8,500 c.c. was in the 24 hour period in which the output was 12,000 c.c. and the weight loss 15 pounds.\* He tolerated 1,000 c.c. of isotonic dextrose by vein while the venous pressure was 22 cm. (30 cm. with liver pressure), the venous pressure dropping as indicated.

The most marked diminution in edema occurred during the second day when there was no weight loss, indicating a marked "shift" of water to the cells; a lesser "shift" is indicated after the first six days by the disappearance of the remaining detectable edema without weight loss. The last two doses of mercupurin shown were given as tests for occult edema.<sup>61</sup> (If there is no weight loss or if the weight loss is promptly regained it is good evidence that occult edema no longer exists; here it confirmed the impression that the residual splenomegaly and hepatomegaly were due to the leukemia.)

Here again is seen the preservative suppression of urine chloride excretion which followed mercury-induced outpourings, and the ability of the kidneys to eliminate *unnneeded* plain water without *needed* salts. Thus, on the first day 46 grams of sodium chloride are recorded in 6.6 liters and on the sixth day 45 grams in 11.9 liters of water, and on the seventh day less than 4 grams appear in 6.5 liters of urine water, in spite of the daily ingestion of about 6 grams of chloride salts. Nor does a *high intake* of plain water overwhelm this selective function of the kidneys and "wash out" needed electrolyte, for on the seventh day with an intake of 7.5 liters and on the twelfth day with an intake of 8.0 liters the urinary sodium chloride remains less than 5 grams. In the 16 days of the period the plasma chlorides changed from 594

\* The crude water balance figures for the 16 days here are representative: the total intake of water as such was 93.0 liters and the total urine water output was 93.9 liters, indicating that all of the 40 pounds of the edema fluid water, 18 liters, plus about 13 liters of the water of the solid food in the diet, or a total of about 30 liters of water, must have left the body as water of vaporization (except for about 3 liters eliminated via the stool), implying a quite reasonable water vapor loss of about 1,700 c.c. daily.



to 648 mg., the  $\text{CO}_2\text{CP}$  from 59 to 71, the serum proteins from 5.7 (3.7) to 6.2 (4.0) grams and the hematocrit from 36 to 52 per cent.

In November there still had been no recurrence of edema in spite of too great activity. By February edema had begun to recur after a five weeks' lapse from the régime, and it was imperfectly controlled at his ranch home until death, in September 1942, from leukemia.

*Comment.* Here longstanding brawny anasarca and tight ascites, which are hard to relieve, were cleared in spite of age, advanced hypertensive and arteriosclerotic changes, poor renal function and other complications; and both cases tolerated 1,000 c.c. of isotonic dextrose by vein, at a time when the venous pressures were above 20 cm. of blood.<sup>34, 35</sup> The impaired kidneys of these cases appeared capable of protecting the concentration and the electrolyte pattern of the extracellular fluid in spite of forced diuresis from mercurial diuretics.<sup>1, 18, 21</sup>

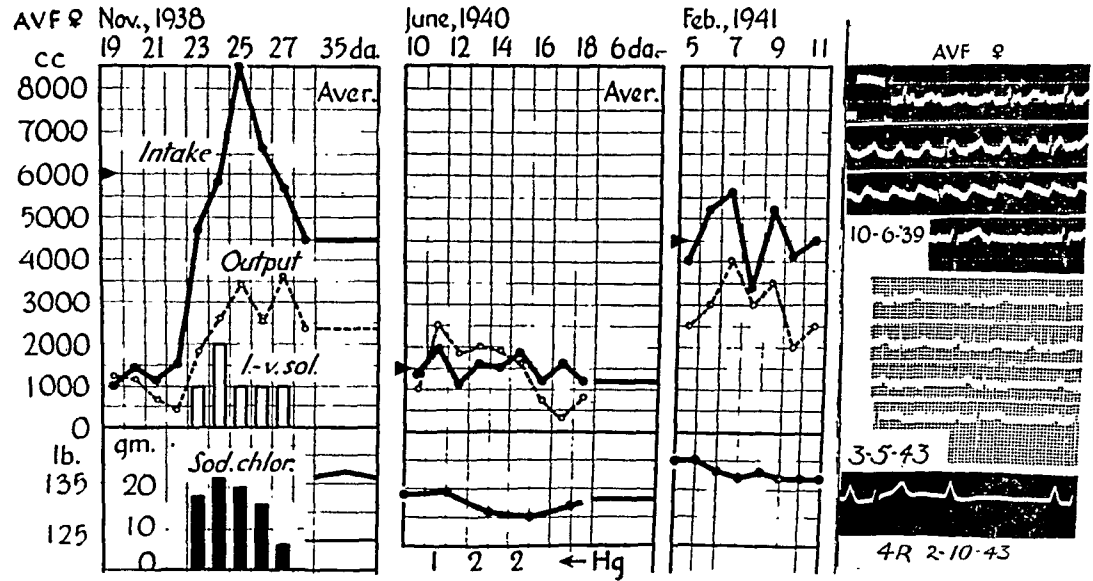


FIG. 5. Salt replacement with a high water intake in advanced heart disease.

Figure 5. Salt Replacement with a High Water Intake in Advanced Heart Disease: \* This patient was a veteran of 12 years of recurrent congestive heart failure prior to 1938, when she was admitted in a critical state from a *chloride deficit* and a loss of body fluid volume. She was given 80 grams of salt with 30 liters of water in five days and tolerated an average daily intake of 4,500 c.c. for 36 more days without the production of edema. At the time of the three admissions shown here no gross peripheral edema was present, but there were such signs of passive congestion of the lungs

\* The two periods of treatment on a high fluid intake shown here (and the 1940 period for V. J. B. shown in figure 3) serve as examples for about half of the 233 periods from the 161 cases with No Gross Edema in which no edema was produced during treatment on the high fluid régime, in spite of the prior existence of gross edema or its subsequent appearance when off the régime (table 1).

and liver that it was thought proper elsewhere, as is shown in the *June 1940 admission*, to place her on a restriction of fluids and use a mercurial diuretic in accordance with accepted practice.\*

*Case 158.* A. V. F., ranch housewife, age 43 in 1938, had rheumatic fever in 1922, her first congestive failure with hemoptyses and marked edema of the ankles in 1926, and arrhythmia and syncopal attacks from 1931 on. In 1926, 1940, and 1943 she was seen at the Mayo Clinic, where the mitral stenosis and aortic stenosis, moderate congestive failure and "serious organic heart disease with marked cardiac crippling" were noted.

The electrocardiogram of October 6, 1939, in the figure is characteristic of many taken from 1938 through 1943, showing an auricular flutter (rate 240 per minute) and a slow irregular ventricular beat, the rate varying from 35 to 70 per minute, quite unaffected by digitalis. In the three standard leads the QRS complexes do not exceed 5 millivolts in height and the flutter waves are large and notched. The March 5, 1943 tracing shows a transient period of normal rhythm and a P-R interval of 0.24 second without digitalis. On February 10, 1943, during a syncope at the Mayo Clinic, Wenckebach periods were caught in their lead 4R, the P-R intervals varying from 0.32 to 0.40 second.

She was first seen here on November 23, 1938, when salt replacement therapy was required, as shown in the first column of this figure and as described below. The data from the *June 1940 admission* are shown in the center column to contrast the high intake of this régime with the low intake of the accepted régimes, which included also potassium nitrate, the restriction of salt, and a course of mercurial diuretics. For a year and a half prior to the June admission there, she had controlled edema and been active on the high fluid régime with a measured intake of 3,000 to 5,000 c.c. daily. But in July 1940, while on the restricted fluid régime at home, she developed marked edema with a gain of nine pounds in two weeks, which she cleared at home by voluntarily returning to the high fluid régime. The *February 1941 admission* (right hand column), for mild respiratory infection, shows that she continued to tolerate without the production of edema an average daily intake of 4,500 c.c. with no mercurial diuretics and only 2 grams of ammonium chloride daily. (In the winter of 1943 she was again advised, on the basis of accepted practice, to restrict fluids, but she continued with the high fluid régime because, she said, "I feel better and can keep the swelling down easier." That fall she cleared at home the massive edema of the legs, that developed while riding a combine during the 1943 harvest, by attention to her régime.)

The *November 19, 1938 admission*: During the preceding six months massive edema had occasioned hospitalization with accepted methods of treatment for three weeks in June, and for five weeks ending November 5. Only two days before admission on November 19, her legs had been badly swollen but the edema had disappeared coincident with frequent emeses during the 12 hours before admission. During the first four days in the hospital her condition was regarded as terminal; there was an occasional small emesis, she became too weak to move in bed without help, and the heart sounds were so feeble that the characteristic murmurs of mitral stenosis, aortic stenosis, and aortic regurgitation, which became apparent later, were not heard. The average intake of these first four days was 1,200 c.c. daily.

When she was seen on November 23, neither the history nor the electrocardiogram (identical with tracing of October 6, 1939) suggested digitalis intoxication. The

\* The clinical data in the periods of treatment with restriction of fluids, shown in figures 5, 6, 7 and 8, were made available through the courtesy of Drs. A. M. Snell, A. R. Barnes, T. J. Dry, H. L. Smith, R. L. Parker and M. N. Keith; and the microscopic findings of autopsy material from the cases in figures 7 and 8 were confirmed by Dr. J. W. Kernohan.

blood urea was 54 mg. and the maximum specific gravity of the urine 1.015. The clinical impression of hypochloremia was confirmed by a plasma chloride reading of 320 mg.

Because of the edema present only two days before admission, she was placed on a liquid neutral diet so that the ingestion of salt could be better gauged. It was estimated that she would require about 76 grams of salt. By the end of 48 hours, after 40 grams of salt had been taken with 10.5 liters of water, she showed improvement in general strength and in the quality of the heart sounds. By the end of the fifth day of replacement she had received 80 grams of salt with 30 liters of water, the plasma chlorides had risen to 500 mg., and she sat up in bed and wrote a letter. There was steady improvement during these five days and no detectable evidence of the development of edema, in spite of the ingestion, on the third day alone, of 20 grams of salt and 8.5 liters of water. During the following 36 days she improved steadily while tolerating an average intake of 4,500 c.c. daily; the weight changed only from 137 to 136 pounds and no edema developed.

The 30 liters of water with 80 grams of salt received in the first five days were the equivalent of 9 liters of normal saline and 21 liters of plain water and this ratio of 1 to 2.3 permitted the correction of the chloride deficit, the total body-fluid deficit and any plain-water deficit present, without the production of edema. The urine output which had fallen to less than 500 c.c. in 24 hours before the high intake was begun, averaged 3,000 c.c. daily the last four days of the replacement period. The extra plain water here did not "wash out" needed sodium or chloride but only assisted the kidneys in regulating the electrolyte pattern accurately and in bringing the extracellular fluid just up to its normal volume.

*Case 289.* M. N., female, age 59 in 1941, presented a similar replacement problem with a *sodium deficit*. She received in the first six days 160 grams of salt (and a few grams of sodium bicarbonate) with 35 liters of water including 5 liters by vein the first day and 3 to 4 liters by vein daily for the next five days. Thus she was given the equivalent of 18 liters of normal saline solution and 17 liters of plain water. She recovered and no edema was produced, Adams-Stokes attacks ceased and the carbon dioxide combining power rose from 28 to 60 volumes per cent, while the plasma chlorides remained unaltered at 500 mg.

*Comment.* Such cases show that, when sodium ingestion is properly regulated, a very high intake of water, with salt as *needed*, does not produce edema even in patients with advanced disease who have had marked edema before.

It appeared that the excess intake of water, with relatively little salt, merely helped the kidneys to correct existing chloride or sodium deficits.<sup>1, 3, 7</sup> It was also noted that when the kidneys could no longer correct such deficits on this high fluid régime they could not correct them with an excess of salt or with the restriction of fluids, and that these latter measures only produced edema or dehydration (figure 7). Finally, it was observed that when such deficits existed in edematous patients and their edema began to clear, the kidneys often kept back enough of either sodium or chloride from the sodium chloride of the edema fluid to correct the existing deficit (figure 4). In replacement therapy here, therefore, no extra salt is given in the presence of marked edema, unless the electrolyte pattern is profoundly disturbed; and,

in all situations where salt is badly needed, more plain water is given in proportion to salt than is present in a normal saline solution.\*

Figure 6. Failure of the High Fluid Régime to Clear Edema: Eventually cases of advancing degenerative disease will reach a stage where they will not clear edema on any régime, although fortunately most of them die

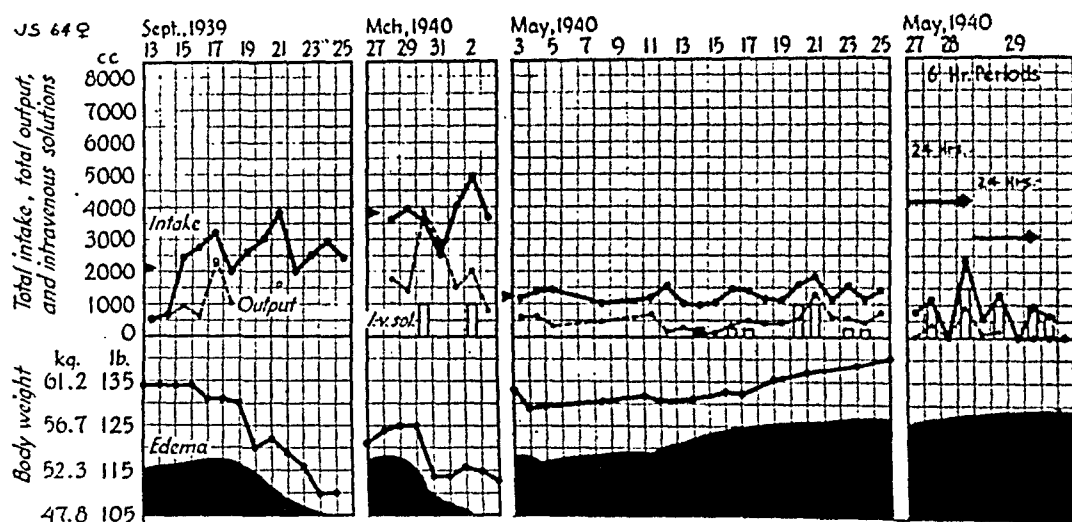


FIG. 6. Failure of the high fluid régime to clear edema.

edema free before this stage is reached. This case illustrates the futility of therapy in such cases on any régime.

*Case 91.* J. S., housewife, age 64 in 1939. In 1926 the blood pressure was 180 mm. Hg systolic and 140 mm. diastolic, and in 1929 the occurrence of an acute myocardial infarction was confirmed by an electrocardiogram. In 1934, after another severe infarction, she developed diabetes mellitus which she neglected, and she showed a constant moderate albuminuria. She was hospitalized three times in 1939 for attacks of coronary occlusion and left ventricular failure and responded well to the high fluid régime with, for example, an average daily intake of 5,000 c.c. for 24 days in June. She did not follow her diet in the intervals and coöperated poorly in the hospital.

*The September 1939 admission:* For the first three days while she was on a low-salt diabetic diet yielding an excess of *basic* ash her weight remained stationary and edema increased until a right hydrothorax became evident. In the next four days, after the change to the neutral diet with its excess of *acid* ash, the edema began to yield reluctantly and she lost 15 pounds. In the next five days, after two grams daily of ammonium chloride were begun, there was a further weight loss of 10 pounds with complete clearing of the edema and hydrothorax. No mercurial diuretic was used.

*In the March-April 1940 admission,* here, she still tolerated a high fluid régime with benefit, for she cleared her edema with a 12 pound weight loss in four days on an average intake of 4,000 c.c. daily.

\* For therapy by vein, the minimum proportion is thought to be one part of plain water as isotonic dextrose to one part of normal saline solution, and the optimum proportion is thought to approach two or even three parts of plain water to one part of normal saline.

In the *May 1940 admission*, however, a month later, at the Mayo Clinic, with her advancing disease nearing its terminal stage, she failed to respond to 23 days of restricted fluids and other accepted measures. She received no extra salt in the little food she took, potassium nitrate was given as tolerated, and the average intake was 1,200 c.c. daily. The edema increased steadily, the blood urea rose from 40 to 110 mg., and there was some loss of vision with the appearance of fresh retinal hemorrhages. During the last 12 days her weight increased 10 pounds in spite of seven intravenous injections of hypertonic dextrose (20 per cent), and one of salyrgan.

Thirty-six hours after leaving there an attempt was made to enforce the high fluid régime here, as shown in the last *May admission* column: (the data for the 60 hours are recorded in six-hour periods). The blood urea was 120 mg. on admission, and mild uremic convulsions occurred at intervals throughout the 60 hours. The clinically severe dehydration was not perceptibly relieved in the first 24 hours by a total intake of about 4,000 c.c., the edema increased a little, and there was no real clinical response except that she roused enough to take a little liquid orally and one neutral feeding. At 2:30 a.m. in the seventh six-hour period, an acute myocardial infarction occurred, following which the signs of anoxemia were unrelieved by the oxygen. In the next 12 hours catheterization yielded only 40 c.c. of urine; yet during the 12 hours she tolerated 1,000 c.c. and 500 c.c. of isotonic solution by vein without incident. Death occurred seven hours after the last 500 c.c. venoclysis, in the midst of a mild convulsion, with a swiftly terminal pulmonary edema.

*Comment.* This patient as she neared the end of her illness, after several years of response to a high fluid régime, did not respond to a restricted fluid régime or to the final attempt to enforce the high fluid régime. This period shown is similar to many that make up the 24 instances in this series of complete failure of the high fluid régime to clear edema or relieve symptoms.

Figure 7. Chronic Glomerular Nephritis with the Nephrosis Syndrome and Cardiopathy: This case fulfilled the usual clinical criteria for nephrosis. The patient was followed from the insidious appearance of massive edema to autopsy; for two years his edema and the degenerative vascular complications were treated on the high fluid régime.

*Case 203.* F. O. G., male, was a long-distance truck driver, age 35 in 1940. His father died at age 65 of "dropsy" and his mother at age 56 of "heart failure." He had had frequent sore throats in childhood, and influenza in 1918. He was underweight but there was no detectable evidence of disease in November 1937 on examination at a medical center where his blood pressure was 100 mm. Hg systolic and 50 mm. diastolic, and his urine showed no albumin and a specific gravity of 1.026.

He was seen here, in May 1940, as an out-patient, because of swelling of the legs of two weeks' duration which followed an acute respiratory infection. The diagnosis of the referring physician, glomerular nephritis, was confirmed; a large amount of albumin and many casts were present in the urine, the fasting blood-urea was 67 mg., enlargement of the heart was noted, and the maximum specific gravity of the urine (corrected for albumin) was 1.010.

Six weeks later, as shown in the *June 1940 admission* at the Mayo Clinic, he was treated as a case of nephrosis. The edema had increased, the blood pressure range was 140 mm. Hg systolic and 90 mm. diastolic to 190 mm. systolic and 110 mm. diastolic, the blood urea ranged from 42 to 52 mg., the serum sulphate was 6 mg., the urea clearance was 30 c.c. The plasma proteins were 3.8 (2.2) grams on

the first day and 3.5 (2.2) grams on the last day of treatment in spite of a diet protein of from 100 to 120 grams. The fluid intake averaged 1,400 c.c. daily, the diet had no added salt and either 18 grams of potassium nitrate or 9 grams of potassium chloride were given daily. Because of very slight decrease in edema and a weight loss of only two and one-quarter pounds in the first five days, 500 c.c. of a 6 per cent solution of acacia were given on the sixth and eighth days, which was followed by an additional weight loss of 10½ pounds and the disappearance of edema by the twelfth day.

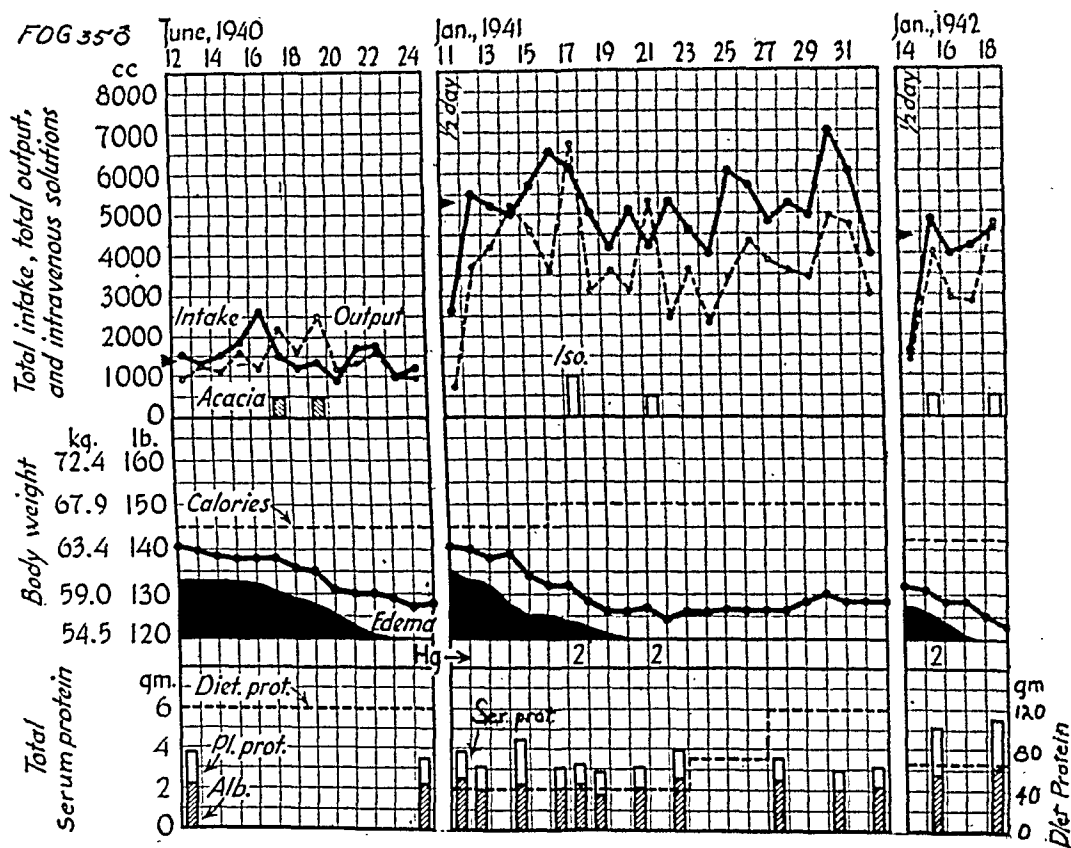


FIG. 7. Chronic glomerular nephritis with the nephrosis syndrome and cardiopathy.

He returned to his work as a trucker, the evening edema of his legs returning in a few weeks. A month before the next admission, swelling of the abdomen and dyspnea forced him to stop work; but his edema increased in spite of rest, although he followed his restricted fluid régime as faithfully as he later followed the high fluid régime.

In the *January 1941 admission* here, after six months on a régime which had restricted water to five glasses a day, he showed marked peripheral edema, with pitting to the sacral region, marked ascites and moderate bilateral hydrothorax. The heart was larger than in May 1940, and the retinal vessels were narrow and tortuous although no retinal hemorrhages were present.

During the 22 days here, the average daily intake was 5,200 c.c., the maximum in one day 7,000 c.c. Instead of 6 grams of potassium nitrate daily and the low-salt, high-protein diet, he received 4 grams of ammonium chloride and 2 c.c. of diluted hydrochloric acid daily, and a neutral diet with 2,500 to 3,000 calories, which yielded only 40 grams of protein daily (as a control observation).

On this régime all the edema cleared in nine days with a weight loss of 15 pounds on an average daily intake of 5,700 c.c. Almost all of the detectable edema disappeared with a nine pound weight loss in the six days before the first test dose of mercupurin, which resulted in six pounds further weight loss, chiefly of occult edema. During the first two and one-half days there was marked decrease in edema with a weight loss of only one and one-half pounds, indicating a shift of water to thirsty cells.

The serum proteins were frequently determined and are shown as columns in the lower tier, the hatched portions representing the serum albumin fractions.\* Note that in spite of the daily loss of from 4 to 20 grams of albumin in the urine, neither the total serum protein nor the albumin fraction changed significantly in the 22 days, whether a high or a low protein diet was given. The serum protein was only 3.9 (2.5) grams on the day of admission, after the six months on a diet protein of 120 grams. After 12 days on a diet protein of 40 grams the serum protein was actually higher, 4.0 (2.6) grams; and after the next 10 days on a maintenance (65 grams) and a high protein diet (120 grams) the serum protein was actually lower, 3.2 (2.2) grams. The albumin fraction of the serum protein ranged from a low of 1.7 grams on the eighth day, by which time the edema had cleared, to a maximum of 2.6 grams on the twelfth day of the low protein diet. Note that the maximum clearing of edema with a weight loss of seven pounds, without the use of a mercurial diuretic, occurred during the fourth and fifth days, while the total serum proteins were falling from their transient high of 4.5 (2.3) grams to 3.1 (2.1) grams.

In the 22 days the hematocrit rose from 35 to 41 on the twelfth day and was 32 per cent on the last day, and the plasma chlorides rose from 540 to 640 mg. The cholesterol dropped from 480 to 232 mg., and the blood urea ranged from 50 to 55 mg. with the diet protein at 40 grams, and from 70 to 75 mg. after the diet protein was increased.

He was able to continue, against advice, his usual heavy work throughout 1941, chiefly because of intelligent management of his diet and régime, which included a measured three quarts of water daily that ensured a total daily fluid intake of 4,000 c.c.

After this year, characteristic vascular complications of his steadily progressing disease brought him into the hospital for four short periods during 1942. Some data from these and his last admission are given below.

The *January 1942 admission* only is shown in this figure. His vision had failed after two weeks of a low fluid intake because of severe headaches with nausea and vomiting. In spite of the presence of an advanced "albuminuric retinitis" with choking of the discs, and paroxysmal dyspnea and basal râles, he tolerated without disaster and with marked clinical improvement an average intake of 4,500 c.c. for five days with the clearing chiefly of occult edema with a weight loss of nine pounds. After a year with a diet protein of 65 grams the serum protein was 5.1 (2.7) grams, and rose to 5.6 (3.1) grams. The hematocrit rose from 34 to 41 per cent, the cholesterol fell from 400 to 294 mg., and the plasma chlorides rose from 632 to 700 mg.

After a similar episode in May 1942 the fundi again showed fresh hemorrhages and choking of the discs. The average daily intake for the eight days was brought to 5,400 c.c. by intravenous supplements of isotonic dextrose of 1,000 c.c. each, given twice daily for six days, without disaster and with clinical improvement. A venous pressure of 14 cm. dropped to 5 cm. by the seventh day. With the diet protein at 40 grams the serum protein rose from 4.2 (2.1) to 4.6 (3.0) grams. There were only trifling changes in the hematocrit,  $\text{CO}_2\text{CP}$  and chlorides. The blood urea ranged now from 105 to 110 mg.

In August, after a low intake due to nausea and vomiting, he was admitted with extreme orthopnea and signs of acute left ventricular failure. Choking of the discs

\* Dr. E. M. Landis kindly reviewed some of the serum protein data in this series.

was not present, but anasarca was marked. The edema cleared and the symptoms were entirely relieved in six days with 18 pounds loss of weight on an average daily intake of 3,000 c.c. With the diet protein at 40 grams and the daily loss of albumin in the urine ranging from 6 to 23 grams, the initial serum protein of 3.5 (1.3) grams rose in 48 hours to 5.2 (3.2) grams, the reversed albumin/globulin ratio becoming normal; on the seventh day the serum protein was 5.3 (3.2) grams. The hematocrit changed from 30 to 36 per cent, the  $\text{CO}_2\text{CP}$  from 47 to 46, the plasma chlorides from 627 to 598 mg., and the blood urea from 123 to 127 mg.

He was admitted again in October for the same complications. He cleared edema with a loss of 14 pounds of weight in four days on an average daily intake of 3,500 c.c. The serum protein of 5.5 (3.3) grams and the hematocrit of 30 per cent remained unchanged, the plasma chlorides changed from 660 to 610 mg., the blood urea ranged from 130 to 190 mg., and the  $\text{CO}_2\text{CP}$ , now low, changed only from 36 to 38 volumes per cent. It was increasingly difficult for him to take fluids or adequate amounts of food.

In January 1943 he was admitted in an obviously terminal state, with pulmonary infarction syndrome; bronchopneumonia developed on the fifth day, and he died on the ninth day.\* No disturbing attempts were made to keep the intake high or to enforce the régime; yet, driven by fever and thirst, until two days before his death he took an average intake of 2,500 c.c. daily, and from 900 to 1,800 c.c. of urine were elaborated daily. Serum proteins were 4.8 (3.3) grams, rising to 5.8 (3.4) on the seventh day and dropping to 5.0 (3.2) grams on the ninth day; and for the same days the hematocrit was 21, 25, and 29 per cent. The blood urea rose from 180 to 215 mg. before death and the plasma chlorides ranged from 594 to 605 mg.

The carbon dioxide combining power was 35.2 on this last admission and 36.8 volumes per cent on the fifth day; during his rapid failure in the last four days it dropped to 25.2 on the seventh day, and in spite of the administration of enough sodium chloride and sodium bicarbonate to increase markedly the moderate edema still present, it was only 28.3 volumes per cent on the ninth day. (In recent quantitative observations on a "dry" nephritic [D. C., age 26] given 60 grams of sodium salts in 48 hours on two different occasions, a carbon dioxide combining power of from 26 to 28 volumes per cent was not affected appreciably, although only one quarter of the extra salt given appeared in the urine; but edema was produced and dehydration became marked.)

*A similar case (204), L. T., male, age 27 in 1938, was followed three years.†* In April 1938 the edema cleared completely with a 20 pound weight loss in 12 days on an average daily intake of 4,600 c.c. In February 1940, with a diet protein of 40 grams and an average daily intake of 4,500 c.c. he lost 10 pounds of weight in eight days while the edema cleared and the serum protein dropped from 4.4 (2.6) to 3.6 (1.6) grams, the hematocrit rising from 29 to 37 per cent. In the next 30 days, in spite of a daily loss of albumin in the urine of from 3 to 18 grams, and with the diet protein still held at 40 grams, the serum protein rose to 5.2 (2.6) grams, the hematocrit dropping to 32 per cent. The plasma chlorides ranged from 570 to 610 grams. Supplements of isotonic dextrose, totaling 2,000 c.c. daily, were given by vein for the first 10 days, yet, in spite of choked discs and retinal hemorrhages on admission, neither pulmonary edema nor convulsions were produced and there was actual improvement in vision as measured by a Snellen chart.

\* Autopsy in brief: Multiple large pulmonary infarctions and superimposed bronchopneumonia; fresh pericarditis with 200 c.c. of fluid; heart grossly enlarged with marked atherosclerosis and calcification of the coronary vessels; fine droplets of fat dispersed throughout the hepatic parenchyma; "typical chronic glomerulonephritis" with involvement of the glomeruli varying from complete fibrosis to swelling and increased cellularity.

† Dr. George Dock confirmed the diagnosis and the effectiveness of the high fluid régime in this case.



*Another case* (213), R. T., male, age 19 in 1940, with severe subacute (glomerular) nephritis was admitted after 24 hours of vomiting. In the face of a maximum specific gravity of the urine of 1.010 (corrected for albumin) his daily intake for 18 days averaged 10,000 c.c., with a maximum intake for one day of 15,000 c.c., and a maximum urine output for one day of 18,000 c.c. In spite of this flood of water through him and his impaired kidneys, the plasma chlorides rose from 462 to 511 mg. without extra salt, and his massive edema cleared completely with a weight loss of 24 pounds in the first eight days.

*Comment.* The observations in this series confirm the notorious resistance to any type of therapy of "nephrotic edema," but indicate that it can be best controlled for a longer time on this high fluid régime, even on the pediatric service where the difficulties of enforcing such a régime are much greater.

With the frequent determinations of the plasma protein percentages it appeared that most of the percentage changes in the plasma proteins are relative and the result of swift fluctuations in the volume of the circulating blood.<sup>20, 21, 25, 60</sup> The studies with the low protein diets suggest that absolute plasma protein defects are more often due to faulty protein metabolism or exchange than to any protein "lack" in the diet or "loss" in the urine, and that such protein defects are corrected more readily, if subject to improvement at all, by some general improvement affecting, for example, liver function, than by a high protein diet.<sup>26, 27, 28, 29</sup>

It was also noted that laboratory determinations made from blood samples were often poor guides to salt replacement therapy, for the plasma chloride and carbon dioxide combining power percentages were often normal when salt was badly needed for *volume* replacement, or were low when extra salt, given in an attempt to correct sodium or chloride deficits in the face of marked impairment of renal function, led only to an increase in edema or to concentration of body-fluid with cellular dehydration. When the renal function was so badly impaired that the kidneys were unable to regulate the electrolyte pattern, the correction of these deficits was effected only by improvement of renal function, when that was possible.<sup>1, 2, 3, 30, 31, 64</sup>

It was noted that left ventricular failure and pulmonary edema and striking eye-ground changes and convulsions (figure 1, also) that had developed during a period of low fluid intake (and not infrequently develop even in non-edematous patients on a restriction of fluids) sometimes disappeared or were greatly improved when the high fluid intake, even with intravenous supplements, was enforced. This suggests that the syndromes of pulmonary, cerebral, and retinal edema are not directly related to the simple volume increase in interstitial fluid that we call edema, anasarca or dropsy, but may be more directly related to cell injury from cell anoxia or even cell dehydration, for example, which are common in serious illness.<sup>2, 6, 31, 32, 33, 39, 40, 47, 58, 64</sup>

In general, plasma protein, electrolyte and capillary bed disturbances were most effectively relieved, when correctible at all, by the minimum re-

quirement of salt and the maximum of plain water; thus, *plain water*, oxygen and small doses of adrenalin by their effect on cell function and circulating blood volume (presumably by improving renal and hepatic function and restoring the tone of the vascular bed) corrected these disturbances more often than large amounts of protein or salt, or a restriction of fluids.

Figure 8. A Case of Progressing Cardiovascular Disease, Managed on Restricted Fluid and High Fluid Régimes: The majority of patients are quite readily freed of their edema in almost any given period of treatment on either type of régime. The most significant observations in this study, therefore, are those which indicate that a high fluid intake régime can relieve edema which has not been relieved by a competently directed restricted fluid régime. (See V. J. B., figure 3, also.)

This case was followed closely for nearly five years, from an acute coronary occlusion until death. His course was marked by continuous unfavorable progress with increasing coronary, myocardial and renal insufficiency and, during the year on restricted fluids, by the development of nephrotic features. He was observed for almost three years on the high fluid régime, then, through the courtesy of an associate, for a year on a restricted fluid régime, and finally, for 10 months again on a high fluid régime.

*Case 128.* H. L. M., male, restaurant manager, age 45 in 1936. His father, 10 years after a hemiplegia, died at the age of 72; his mother was disabled by severe angina at age 65. The patient had anginal pain in December 1935 and ankle edema by the spring of 1936 when he had his first myocardial infarction, with an acute left ventricular failure and a drop in blood pressure from 190 mm. Hg systolic and 135 diastolic to 125 mm. systolic and 90 mm. diastolic, and the electrocardiographic changes of an acute infarction and an atypical left bundle branch block. By October 1937 physical, mental and alcoholic intemperance had brought his edema to the stage of general anasarca with hydrothorax and ascites, which were cleared at home in 12 days on a neutral diet with a measured intake of from 4 to 5 liters daily. Indiscretions induced frequent attacks of angina, left ventricular failure, and recurrences of edema; the latter he recognized by unusual weight gain and cleared by returning to his high fluid régime on his own initiative. With his digitalis he took ammonium chloride and diluted hydrochloric acid, but he found that these were not sufficient to prevent the recurrence of edema or effect its clearing without taking 4,000 c.c. or more of water daily. Until 1939 no mercurial diuretic was used.

The *January 1939 admission* illustrates management in the three years from May 1936 to April 1939. Peripheral edema extended along the abdominal wall and up the back to mid-scapula; bilateral hydrothorax and ascites were present, and the liver edge could be palpated at a hand's breadth below the costal margin. By the end of the first three days there was no weight loss in spite of evident marked loss of edema, as shown by the disappearance of peripheral edema and a marked decrease in the size of the abdomen (indicating a marked shift of water to the cells even during and following a preliminary rehydration weight gain which had amounted to two pounds by the morning of the second day). In the next eight days edema cleared entirely with a weight loss of 20 pounds on an average intake of 4,200 c.c. daily.

His usual indiscretions resulted by April 1939 in a recurrence of massive edema which persisted on a restricted fluid régime until March 1940. During these 11



months he was disabled by anasarca in spite of seven months in the hospital and active treatment by competent internists with the usual measures; which included a sharp restriction of fluids with a low-salt, high-protein diet (120 grams), potassium nitrate, and hypertonic dextrose solutions with salyrgan or aminophyllin by vein. The brawny edema that reached to the waist and the ascites did not respond to therapy even though, for example, in August 1939 he received a diet protein of 140 grams daily with thrice weekly injections of salyrgan and there was a rise in the plasma proteins from 4.0 (2.3) to 5.4 (3.2) grams in 18 days.

The *January 1940 admission* at the Mayo Clinic illustrates the type of restricted fluid régime and intensive therapy used during this year. A few of the significant findings there, in addition to the anasarca and ascites, were: a blood pressure of 182 mm. Hg systolic and 140 mm. diastolic, a few retinal hemorrhages, a plasma protein determination of 6.5 (4.2) grams, albuminuria (grade 2), a blood urea of 50 mg. and a fixed specific gravity of the urine between 1.010 and 1.013. The diagnosis was "diffuse arterial disease with hypertension (group 3), severe myocardial damage and congestive heart failure," and the prognosis was given as "poor." The average daily intake was held at 1,500 c.c., including the hypertonic dextrose solutions, with salyrgan by vein every second day, and with aminophyllin on alternate days. A forced diuresis was evoked with some five pounds net weight loss, but there was very little change in the edema and no relief of his severe paroxysmal dyspnea and orthopnea.

In spite of the continuation of this régime through February the anasarca increased so that within two weeks after leaving there the aspiration of ascitic fluid was necessary, and within three weeks more, aspiration again seemed imperative.

The *March 1940 admission* shows the data of the two weeks' trial on the high fluid régime, requested by his attendant. The abdomen was tightly swollen with ascites and the liver edge was ballottable one finger's-breadth below the umbilicus; there was pitting edema of the abdominal wall and deep pitting up the back as high as the scapulae; bilateral hydrothorax was present. The tight brawny edema of the legs and thighs had been present continuously since April 1939. By the end of 36 hours he was much more comfortable, his thirst was relieved, the abdomen and peripheral edema had softened a little, and the pulmonary râles were decreased; which indicated, since there had been no weight loss, some shift of water to the thirsty cells. On the third day the first dose of mercupurin resulted in a diuresis and a weight loss which continued with two more doses of mercupurin until 28 pounds of weight had been lost in seven days on an average intake of over 5,000 c.c. daily, achieved by 1,000 c.c. supplements of 5 per cent dextrose in distilled water given twice daily. A test dose of mercupurin on the eleventh day eliminated the little occult edema that remained. At the request of his attendant, the diet protein of the neutral diet had been held at 130 grams daily, yet the plasma proteins dropped from 5.8 (4.0) to 4.8 (3.2) grams in 13 days. The hematocrit changed only from 52 to 49 per cent, and the plasma chlorides rose from 528 to 595 mg.

The tight brawny edema and the ascites and hydrothorax were cleared completely for the first time in a year, and his symptoms were so well relieved and controlled that he resumed many activities during the next nine months. In that time he was admitted twice after lapses from his régime.

In the *June 1940 admission* he cleared 20 pounds of edema in seven days on an average daily intake of 6,700 c.c. With the diet protein at 65 grams, the plasma protein rose from 3.6 (2.4) to 4.8 (3.6) grams in two days and 5.3 (3.0) grams by the eighth day. (In August 1939 with the diet protein at 140 grams, there was a rise from 4.0 (2.3) to 5.4 (3.2) grams in 18 days, but without any loss of edema.) There was no evidence of body fluid dilution, the hematocrit readings for the same days being 39, 45, and 50 per cent, and the plasma chlorides 511, 561, and 610 mg.

In the *August 1940 admission* he cleared 15 pounds of edema in five days on an

average daily intake of 6,000 c.c. With the diet protein at 40 grams, the plasma proteins actually rose from 4.2 (2.8) to 5.3 (3.3) grams in the five days; the hematocrit rose from 40 to 52 per cent, and the plasma chlorides dropped from 590 to 544.

During his last four months he adhered to his régime and did not have to re-enter the hospital; he spent from 10 to 12 hours a day at his restaurant before his sudden death at home late in December of 1940.\*

*Comment.* Most of us have been taught to regard such brine-logged patients as water-logged and we can therefore appreciate Sir Thomas Witherly's<sup>41</sup> remarks on the case which he reported to the Royal College of Physicians about 1690: "A Wine-Cooper fell into a Dropsy which resisted all the usual Methods.† This Man was prodigiously swell'd, Belly, Back, Sides, Thighs and Legs. Being past all Hopes and having on him an inextinguishable Thirst, he was permitted to drink 14 Quarts of Water in about 10 Hours and in all that Time made not one drop of Urine. Soon after he began to piss; and he drank on, 4 or 5 Quarts daily, and so recovered. . . . That Water should expell Water is a Miracle beyond any of St. Winifred's. Now no Man in his Senses would have prescribed such a Water course to cure a Dropsy, which shows how little we know of Nature and the great Uncertainty of our Art."

#### RECAPITULATION

A high fluid intake was given, with the *proper* regulation of sodium, to edematous patients with:

- Severe acute injury of the myocardium,
- Marked narrowing or incompetence of the heart valves,
- Advanced general vascular disease,
- Eclampsia and preëclamptic toxemias and
- Advanced nephritis with the nephrosis syndrome.

This was often in the face of high venous pressures or low plasma proteins, and even in spite of the presence on admission of such findings as:

- Acute pulmonary edema,
- Convulsions or choked discs,
- Low fixed specific gravity of the urine or
- Marked chloride or sodium deficits.

The common objections to a high fluid intake were not sustained by the observations, for clinically a large intake of plain water on this régime did not:

- "Overwork" the heart or "overburden" the circulation,
- Produce generalized edema or retard its disappearance,

\* At autopsy the chief significant findings were: the greatly enlarged heart with marked sclerosis of the coronary vessels, multiple old myocardial infarctions with fibrosis and thinning of one area of the left ventricular wall. On sectioning the other organs, the knife felt as though it were passing through fine wet sand; diffuse arteriolar sclerosis was present in every organ, most advanced in the arterioles of the lungs and of the kidneys.

† The "usual methods" besides purges and vomits, included the use of calomel, mineral acids and the muriate of ammonia, but not a free use of water, even from Winifred's Well.

Act adversely with high venous pressure or low plasma proteins,  
 Produce pulmonary edema or convulsions,  
 Produce so-called "water intoxication" (body fluid dilution),  
 "Wash out" needed sodium or chloride, or  
 Hinder restoration to normal of lost body fluid volume or  
 The correction of electrolyte pattern defects.

On the contrary, it was observed that such cases and such conditions tolerated the large amounts of water of the régime without disaster and with immediate and late results superior to those obtainable on accepted restricted fluid régimes.

### SUMMARY

1. The effects of a régime, in which a very high fluid intake was enforced, on patients with edema and cardiac disease are reported, as observed and studied for eight years in 626 separate periods of treatment of 402 cases. The method used in the study is outlined, the material is analyzed, and some of the general and specific observations are presented.

2. It was observed that patients with marked edema, particularly the 94 per cent with gross cardiopathy, tolerated the high fluid intake with impunity and that the results were better than those formerly obtained with the restriction of fluids.

3. It is suggested that the régime used is physiologically sound and that it is clinically useful in the correction and prevention of the intimately related phenomena of edema, oliguria or anuria and dehydration, wherever they are encountered or anticipated.

4. The observations appear to call for a critical reëxamination of the accepted clinical practice of the restriction of fluids in the presence of edema, and of the accepted hypotheses regarding edema formation and congestive heart failure upon which this practice is based.

### APPENDIX ANALYSIS OF MATERIAL \*

TABLE IV

Primary Disease Groups	Gross Edema	No Gross Edema	Totals
Arteriosclerotic and hypertensive heart disease.....	83	51	134
Acute myocardial infarction.....	40	59	99
Advanced general vascular disease with cardiopathy.....	21	4	25
Cor pulmonale and thyrogenic heart disease.....	10	11	21
Rheumatic heart disease, chronic valvular.....	48	22	70
Nephritic syndromes.....	23	3	26
Miscellaneous cases with edema and/or cardiopathy.....	16	11	27
Total number of cases.....	241	161	402

\* Table 3, which listed all of the 402 cases of this series and showed the data most pertinent to this study from 575 of the 626 separate periods of observation, is omitted here for lack of space and paper. (It will be included with the reprints.) Its data are summarized in tables 1 and 2 above and in the tables below.

The cases in the second line are arbitrarily separated from those in the first line, and there were 15 more patients with acute myocardial infarction in the other groups. In the advanced general vascular disease group are included seven cases of malignant hypertension. The rheumatic heart disease cases include 12 with acute rheumatic pancarditis and four with sub-acute bacterial endocarditis (*Streptococcus viridans*). The nephritic syndromes included were not mild, 20 of the 26 showed evident cardiopathy, and 10 fulfilled the ordinary criteria for nephrosis. In the 11 miscellaneous cases with no gross edema there were three with congenital heart disease (a patent ductus arteriosus, a coarctation of the aorta, and a dextrocardia, with bundle branch block), and two toxemias of pregnancy; the 16 cases with gross edema are described further in table 6.

TABLE V  
Some Complications Which Tolerated the Régime

Findings	Instances
Retinal edema and/or hemorrhages.....	38
Advanced retinitis with choked discs.....	16
Major convulsions.....	11
Acute left ventricular failure or pulmonary infarction.....	36
Acute profuse pulmonary edema.....	18
A maximum specific gravity of the urine below 1.016.....	51

These findings were present at the time of admission. Retinal edema with or without hemorrhages was present 15 times, and fresh retinal hemorrhages 32 times. In addition, retinal sclerosis with old hemorrhages was noted 24 times. In the 16 patients with choked discs, the visual acuity in seven actually improved. The 11 admitted with major convulsions recovered without recurrences; four were eclamptics. In addition, 17 patients with Adams-Stokes attacks and 29 admitted following cerebral accidents (including four with meningeal hemorrhage and xanthochromic spinal fluid) were treated; and seven other cases admitted after arterial emboli cleared edema. (Emboli occurred twice during treatment in patients who were fibrillating.)

Acute left ventricular failure was present in 12 instances, gross profuse hemoptyses in 10, and the syndrome of pulmonary infarction in 24 instances. Acute pulmonary edema with the profuse expectoration of thin bloody froth was present on admission in 18 instances and improvement was not retarded by the generous intake of fluid. Pulmonary edema occurred three times during therapy (see Untoward Reactions). In addition, in 37 instances hydrothorax reaching to mid-scapula was cleared completely without aspiration.\*

\*Hydrothorax was aspirated only 10 times in the 393 periods of treatment; in three for bloody effusion in rheumatic fever and in two for diagnostic purposes. Ascitic fluid was aspirated only nine times; in three of these instances before therapy was started. Thus, aspiration for either was done for relief of symptoms after therapy was begun, only 11 times in the eight years of the study.

In 51 instances the maximum specific gravity of the urine was below 1.016, as determined on admission when dehydration and oliguria were marked or later by a concentration test. (In such cases the daily intake was held at about 5 liters to insure about 3 liters of urine-water.<sup>1</sup>) Marked oliguria or anuria was encountered 53 times with acute myocardial infarction; nine patients with only one kidney (three newly operated) and two cases of advanced bilateral congenital hydronephrosis tolerated the régime well. Of 41 patients admitted in severe uremia about half responded well, usually with large intravenous supplements (in some a blood urea of over 300 mg. became normal).

Other conditions which served to test the régime were: auricular fibrillation and/or flutter in 73 cases; both mitral stenosis and aortic insufficiency in 19; either mitral stenosis or aortic insufficiency in 60; heart block complete and permanent in 12; pregnancy beyond the first trimester in 16, and a major operation during the period of observation in 21.

Table 6 indicates to what extent the effect of the régime was observed on the more resistant forms of edema, not infrequently in the face of a rapidly fatal outcome from the primary disease. The average ages and the sex incidence for the various groups were characteristic of any similar series.

TABLE VI  
Groups of the 241 Cases with Gross Edema

		Main Groups			
		Cases	Male	Female	Average Age
Simple hypertensive and arteriosclerotic heart disease.....	70				
Acute myocardial infarction.....	40				
Resistant ascites, with cardiopathy.....	13				
Advanced general vascular disease.....	11				
Diabetes mellitus with anasarca.....	10				
Cor pulmonale (7), Thyrogenic ht. dis. (3).....	10				
Heart Disease, Degenerative, Progressive.....	Totals	154	84	70	60.9 yrs.
Mitral stenosis and/or aortic insufficiency.....	38				
Same, with acute rheumatic pancarditis.....	6				
Same, with viridans endocarditis.....	4				
Heart Disease, Rheumatic, Chronic Valvular.....	Totals	48	14	34	41.6 yrs.
Nephrosis.....	10				
Acute and subacute nephritis.....	13				
Eclampsia (5), lymphoblastoma (5), pernicious anemia (3), other cases (3).....	16				
Renal Disease and Other Cases.....	Totals	39	19	20	34.0 yrs.
Gross Edema Cases.....	Totals	241	117	124	52.5 yrs.

The 13 cases with resistant ascites had features of cirrhosis of the liver in addition to cardiopathy; all had been aspirated before admission, some repeatedly; their livers were very large or very small, and there was a history of alcoholism in nine of the 12 men. The average age for the ad-



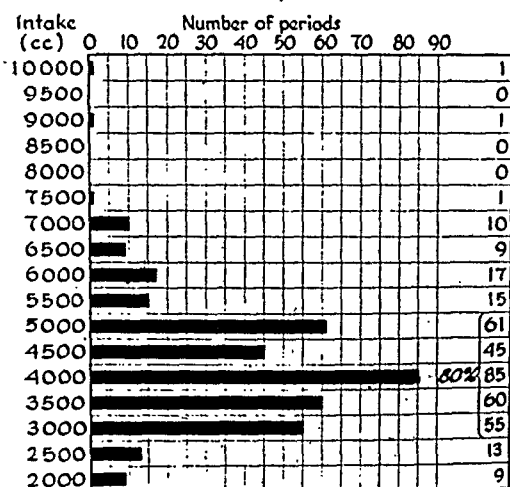
vanced general vascular disease group was only 41 years; three of these had the syndrome of malignant hypertension. The 10 cases with diabetes mellitus had had their self-neglected diabetes for from nine to 20 years and had developed the peculiarly resistant anasarca with nephrotic features common to such cases (average age 54.4 years, 10 years less than the average age for the first three sub-groups).

In the rheumatic heart disease group, edema and pleural effusions were controlled in six cases of acute pancarditis, and edema was controlled in four cases dying of subacute bacterial endocarditis (proved at autopsy or by blood cultures of *Streptococcus viridans*).

TABLE VII

Frequency Distribution of 393 Periods of Treatment in 241 Cases with Gross Edema

In relation to average\* daily intake (382 periods)



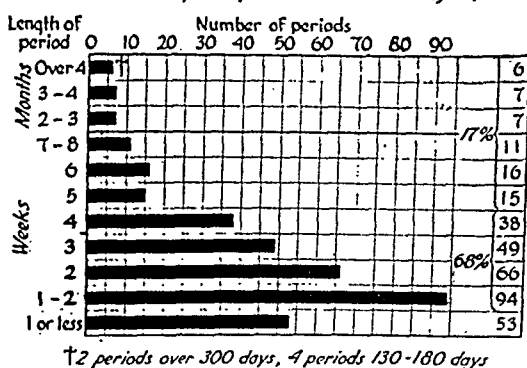
\* MAXIMUM INTAKES in 24 hr., recorded in 364 periods:  
 4000 to 7000 cc in 290 periods (80%)  
 Above " " " 55 "  
 " " " " 5 "

ISOTONIC INTRAVENOUS SUPPLEMENT  
 given over 2000 times in 194 periods, 132 cases

Single volumes i.v. 500 to 2000 cc  
 Total volume, 24 hr. 500 to 8000 cc  
 Rate 500 cc in 1 hr., up to 2000 cc in 1½ to 2 hr.

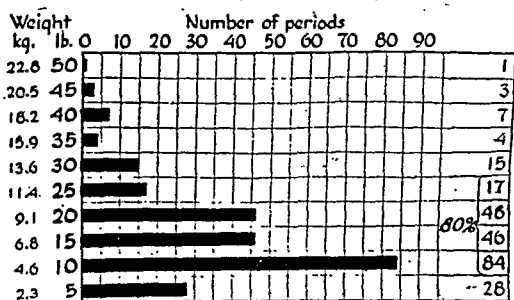
Maximum use examples: 2000 cc vol. b.i.d. for 24 days  
 3000 to 6000 cc total daily " 34 "

In relation to length of period of treatment (361 periods)



\* 2 periods over 300 days, 4 periods 130-180 days

In relation to weight loss (251 periods)



In some of the 10 cases that showed the resistant edema and the accepted criteria of nephrosis low-protein diets were used. The 13 acute and subacute nephritis cases were all very ill and had azotemia; nine had gross cardiopathy, and five "smokey" urine. All the 16 miscellaneous cases cleared marked edema, one had multiple myeloma and one had carcinomatosis with ascites (adenocarcinoma by biopsy).

The average daily intake recorded was from 3,000 to 5,000 c.c. in 306 periods or 80 per cent, and from 5,500 to 7,500 c.c. in 52 periods or 13 per

cent. The *maximum* intake in 24 hours (usually ingested in less than 12 hours) was recorded in 364 periods; 4,000 to 7,000 c.c. in 80 per cent and over 7,000 c.c. in 60 periods or 16 per cent. Isotonic intravenous supplements were given as summarized in the lower left corner of the table.

The lengths of the periods of treatment recorded were from one to four weeks in 68 per cent and over five weeks in 17 per cent; the 15 patients on the régime for from three months to a year showed no evidence of body fluid disturbance.

In 251 periods it was possible to record the edema weight loss, which was from 10 to 25 pounds in 193 periods or 80 per cent, and from 30 to 50 pounds in 30 periods or 15 per cent. Some patients lost edema-weight equal to 50 per cent of their edema-free body weight (figure 3, W. T.). The weight losses recorded are corrected for tissue-weight loss. (It should be recalled that in a dehydrated edematous patient, a shift of water between the cells and extracellular fluid of such magnitude may occur that, with the same degree of edema cleared, one patient may lose 10 pounds, another 20 pounds of weight.)

The analyses of the data from the 161 cases with "no gross edema" similar to those in tables 6 and 7, are not presented here since they do not appreciably affect the statistics for the whole series of 402 cases.

*Acknowledgments.* It was possible to begin and pursue this study only through the generous coöperation and active assistance of the author's associates in the several departments of the Great Falls Clinic. The dietitians of the Montana Deaconess and Columbus Hospitals, and the chief laboratory technician and the nursing staff of the Montana Deaconess Hospital were most helpful. The study benefited particularly by the constant and intelligent efforts of Edith Qualls, R.N., supervisor of the Medical floor since 1936.

The author wishes to thank H. A. Schroeder, E. M. Landis, L. Eichelberger, F. A. Coller, C. C. Sturgis, F. D. Johnston and T. J. Dry for opportune discussion, criticism, or encouragement; and particularly L. H. Newburgh, whose work on the edema of nephritis inspired this study, and to whom the author is indebted for helpful criticism in 1936 and 1939.

#### BIBLIOGRAPHY

1. NEWBURGH, L. H., and LASHMET, F. H.: A comparative study of the excretion of water and solids by normal and abnormal kidneys, *Jr. Clin. Invest.*, 1932, xi, 1003-1009.
2. NEWBURGH, L. H., and LASHMET, F. H.: The importance of dealing quantitatively with water in the study of disease, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 461-470.
3. FREYBERG, R. H., and LASHMET, F. H.: A quantitative study of renal injury in a case of acute poisoning by bichloride of mercury with a note regarding treatment, *Am. Jr. Med. Sci.*, 1935, clxxxix, 392-399.
4. NEWBURGH, L. H., and MACKINNON, F.: The practice of dietetics, 1934, The Macmillan Co., New York, pp. 7-20, 86-97, 225-244, 253-258.
5. ADDIS, T.: The osmotic work of the kidneys and the treatment of glomerular nephritis, *Trans. Assoc. Am. Phys.*, 1940, lv, 223-229.
6. COLLER, F. A., and MADDOCK, W. G.: A study of dehydration in humans, *Ann. Surg.*, 1935, cii, 947-960.

7. COLLIER, F. A., and MADDOCK, W. G.: Water and electrolyte balance, Surg., Gynec., and Obst., 1940, lxx, 340-354.
8. NADAL, S. W., PEDERSEN, S., and MADDOCK, W. G.: Two contrasting types of dehydration, Univ. Hosp. Bull., Ann Arbor, 1941, vii, 53-55.
9. STARLING, E. H.: The fluids of the body, 1900, W. T. Keener & Co., Chicago, pp. 152/154, pp. 163-164, pp. 175-177.
10. DARROW, D. C., and YANNET, H.: The changes in the distribution of body water accompanying increase and decrease in extracellular electrolyte, Jr. Clin. Invest., 1935, xiv, 266-275.
11. HASTINGS, A. B., and EICHELBERGER, L.: Exchange of water and salt between muscle and blood, Jr. Biol. Chem., 1937, cxvii, 73-93. *Ibid.*: 1937, cxviii, 197-218.
12. GAMBLE, J. L.: Extracellular fluid, Bull. Johns Hopkins Hosp., 1937, lxi, 151-197.
13. BEST, C. H., and TAYLOR, N. B.: The physiological basis of medical practice, 1937, Wm. Wood, Baltimore.
14. GOODMAN, L., and GILMAN, A.: The pharmacological basis of therapeutics, 1941, The Macmillan Co., New York.
15. MILBERT, A. H.: Infusion reactions with special reference to "speed shock," Am. Jr. Surg., 1934, xxvi, 479-485.
16. WARTHEN, H. J.: Massive intravenous injections, Arch. Surg., 1935, xxx, 199-227.
17. CUTTING, R. A., ET AL.: Cause of death resulting from massive infusions of isotonic solutions, Arch. Surg., 1939, xxxviii, 599-616.
18. SMYTH, F. S.: Studies in so-called water intoxication, Jr. Clin. Invest., 1930, xii, 55-65.
19. COPE, C. L.: Alkali poisoning (Abst.), Jr. Am. Med. Assoc., 1937, cviii, 336.
20. WARREN, J. V., MERRILL, A. J., and STEAD, E. A., JR.: The role of extracellular fluid in the maintenance of a normal plasma volume, Jr. Clin. Invest., 1943, xxii, 635-641.
21. SEAMAN, B. W., and PONDER, E.: The estimation and control of post-operative dehydration with the aid of hemoglobin and plasma protein determinations, Jr. Clin. Invest., 1943, xxii, 673-685.
22. LANDIS, E. M.: Vascular physiology and clinical medicine, Ann. Int. Med., 1936, x, 290-298.
23. PETERS, J. P., ET AL.: Total acid base equilibrium of plasma in health and disease, X, Acidosis of nephritis, Jr. Clin. Invest., 1929, vi, 517.
24. MOORE, N. S., and STEWART, H. J.: Variation of specific gravity of plasma of blood and the means available for altering it, Jr. Clin. Invest., 1930, ix, 423.
25. STEWART, H. J.: Mechanism of diuresis; alterations in specific gravity of blood plasma with onset of diuresis in heart failure, Jr. Clin. Invest., 1941, xx, 1-6.
26. WHIPPLE, G. H.: Protein production and exchange in the body, including hemoglobin, plasma protein and cell protein, Am. Jr. Med. Sci., 1938, cxcvi, 609-621.
27. STADLER, H., and STENGER, D.: A case of Pick's syndrome as the basis for a study of hypoproteinemia, Jr. Pediat., 1941, xviii, 84-94.
28. JACOBSON, S. D.: The effect of phlebotomy on the blood volume, read at the meeting of The American Federation for Clinical Research, Chicago, Nov. 4, 1943 (unpublished).
29. LYONS, R. H., JACOBSON, S. D., and NEERKIN, J.: The relationship between changes in the plasma volume and changes in the hematocrit and serum protein concentrations, Proc. Central Soc. Clin. Res., 1943, xvi, p. 17.
30. ROWNTREE, L. G., ET AL.: The effects of experimental passive congestion in renal function, Arch. Int. Med., 1913, xi, 120-147.
31. TOTH, L. A.: Urine excretion during anoxia from normal and denervated kidneys in dogs with and without adrenal glands, Am. Jr. Physiol., 1940, cxxix, 532-538.
32. LANDIS, E. M.: Micro-injection studies of capillary permeability: III. The effect of lack of oxygen on the permeability of the capillary wall to fluid and to plasma proteins, Am. Jr. Physiol., 1928, lxxxiii, 528.

33. CUSICK, P. L., BENSON, O. O., JR., and BOOTHBY, W.: Effect of anoxia and high concentration of oxygen on the retinal vessels, *Proc. Staff Meet. Mayo Clin.*, 1940, xv, 500.
34. ALTSCHULE, M. D., and BLUMGART, H. L.: The circulatory dynamics in tricuspid stenosis, *Am. Heart Jr.*, 1937, xiii, 589-598.
35. WIGGERS, C. J.: Cardiac adaptations in acute progressive anoxia, *Ann. Int. Med.*, 1941, xiv, 1237-1247.
36. POLL, D., and STERN, J. E.: Untoward effects of diuresis (with special reference to mercurial diuretics), *Arch. Int. Med.*, 1936, lviii, 1087-1094.
37. TYSON, M. C.: Danger of intravenous mercurial injections in nephrosis, *Jr. Am. Med. Assoc.*, 1941, cxvii, 998-999.
38. DICK, M. W., WARWEG, E., and ANDERSCH, M.: Acacia in the treatment of nephrosis, *Jr. Am. Med. Assoc.*, 1935, cv, 654-657.
39. WILSON, D. M., and SUNDERMAN, F. W.: Studies in serum electrolytes; XII. The effect of water restriction in a patient with Addison's disease receiving sodium chloride, *Jr. Clin. Invest.*, 1939, xviii, 35.
40. ANDERSON, W. A. D., and BETHEA, W. R.: Renal lesions following the administration of hypertonic solutions of sucrose, *Jr. Am. Med. Assoc.*, 1940, cxiv, 1938.
41. WITHERLY, SIR THOMAS, cited in SIR JOHN FLOYER and EDW. BAYNARD'S *History of cold bathing both ancient and modern* (4th ed.), 1715, Wm. Innys, London, ii (Baynard), pp. 449-454.
42. BAKER, SIR GEORGE: *Medical transactions*, 1772, ii (Article xvii), p. 235, published by the Royal College of Physicians.
43. WITHERING, WILLIAM: An account of the foxglove (1785) in the miscellaneous tracts, 1822, Longman, et al., London, ii, p. 127, 137, 287 and 289.
44. MILMAN, SIR FRANCIS: *Animadversions on the nature and cure of the dropsy*, 1786, J. Walker, London, p. 122.
45. DARWELL, JOHN: Dropsy, in John Forbes' "*Cyclopedia of practical medicine*," 1845, Lea and Blanchard, Philadelphia, p. 720.
46. FLINT, AUSTIN: In Napheys' *Modern medical therapeutics* (5th ed.), 1878, D. A. Brinton, Philadelphia, p. 418.
47. FLINT, AUSTIN: *A treatise on the principles and practices of medicine* (6th ed.), 1886, Lea Bros. and Co., pp. 33, 64: 873.
48. OSLER, W.: *Principles and practice of medicine* (2nd ed.), 1896, D. Appleton, New York, p. 787.
49. CHRISTIAN, H. A.: In Osler's *Principles and practice of medicine*, 1938, D. Appleton Century Co., New York, p. 1036.
50. LEVINE, S. A.: *Clinical heart disease*, 1936, W. B. Saunders, Philadelphia, pp. 301-302.
51. FARR, L. E.: Conference on therapy; treatment of edema, *Jr. Am. Med. Assoc.*, 1939, cxii, 837-843.
52. WILLIUS, F. A.: Regulation of diet in heart disease, *Proc. Staff Meet. Mayo Clin.*, 1936, xi, 202-206.
53. BINGER, M. W.: General treatment of edema, *Proc. Staff Meet. Mayo Clin.*, 1936, xi, 648-650.
54. BINGER, M. W.: Edema (editorial), *Ann. Int. Med.*, 1941, xv, 617.
55. LEHNHOFF, H. J., and BINGER, M. W.: Treatment of edema of renal origin, *Jr. Am. Med. Assoc.*, 1943, cxxi, 1321-1325.
56. DRY, T. J.: Congestive heart failure: Factors influencing the ultimate prognosis, *Jr. Am. Med. Assoc.*, 1942, cxviii, 263-266.
57. DESNOO, K.: The prevention of eclampsia, *Am. Jr. Obst. and Gynec.*, 1937, xxxiv, 911-939.
58. McPHAIL, F. L.: The toxemias of pregnancy, *Jr. Am. Med. Assoc.*, 1938, cxi, 1894-1897.

59. McPHAIL, F. L.: Water exchange in toxemias, *West. Jr. Surg., Obst. and Gynec.*, 1939, xlvii, 306-317.
60. CHESLEY, LEON C., and ANNITTE, JOHN E.: A study of salt restriction and of fluid intake in prophylaxis against pre-eclampsia in patients with water retention, *Am. Jr. Obst. and Gynec.*, 1943, xlv, 961-971.
61. GOODMAN, J. I., and CORSARO, J. R.: The basal weight level in the treatment of congestive heart failure, *Am. Heart Jr.*, 1943, xxvi, 338-342.
62. SCHROEDER, H. A.: Personal communication, 1939.
63. SCHROEDER, H. A.: Studies on congestive heart failure. I. The importance of the restriction of salt as compared to water, *Am. Heart Jr.*, 1941, xxii, 141-153.
64. SCHROEDER, H. A., and FUTCHER, P. H.: Studies on congestive heart failure. II. Impaired excretion of sodium chloride, *Am. Jr. Med. Sci.*, 1942, cciv, 52-62.
65. JACOBSON, S. D., LEICHTENTRITT, B., and LYONS, R. H.: The effect of acid and alkaline salts on some patients with rheumatoid arthritis, *Am. Jr. Med. Sci.*, 1942, cciv, 540-546.
66. PELNER, L.: The rapid removal of excess joint fluid by acid salts, *Am. Jr. Med. Sci.*, 1943, ccvi, 498-503.
67. SCHEMM, F. R.: A high fluid intake in the management of edema, especially cardiac edema. I. The details and basis of the régime, *Ann. Int. Med.*, 1942, xvii, 952-969.
68. SCHEMM, F. R.: The loss of edema without loss of weight, read at the Meeting of The American Federation for Clin. Research, Chicago, Nov. 4, 1943 (unpublished).
69. CONNELL, W. F.: (Ontario) Personal communication, 1943.  
ASKEY, J. M.: (California) Personal communication, 1943.  
KURTZ, C. M.: (Wisconsin) Personal communication, 1943.  
LYON, R.: The Schemm treatment of chronic heart failure with edema, *Jr. of Med. Assoc. of Alabama*, August, 1944.\*
70. WARREN, J. V., and STEAD, E. A., JR.: Fluid dynamics in chronic congestive heart failure, *Arch. Int. Med.*, 1944, lxxiii, 138-147.
71. STEAD, E. A., JR.: Care of the patient with chronic heart disease, *Med. Clin. of North America*, 1944, xxviii, 381-387.

\* The Lyon reprint available to me does not give volume or page number.—[Author.]

# THE LEUKOCYTE COUNT IN PRIMARY ATYPICAL PNEUMONIA OF UNDETERMINED ETIOLOGY \*

By OVID O. MEYER, F.A.C.P., and ETHEL W. THEWLIS,  
*Madison, Wisconsin*

BRONCHOPNEUMONIA of the type now commonly considered to be virus pneumonia was seen as long ago as 1872,<sup>1</sup> but present day attention was directed to it by much later reports, chiefly those of Gallagher,<sup>2</sup> Bowen,<sup>3</sup> Reimann,<sup>4</sup> Kneeland and Smetana,<sup>5</sup> and Longcope.<sup>6</sup> In recent years, probably because of greatly increased incidence and, to a lesser extent, proper recognition of this condition and the more positive exclusion of pneumonias of other types by detailed bacteriologic study, these atypical pneumonias have been very frequently observed. In the past six years more than a hundred reports relating to this condition have appeared in the literature.

It is generally believed that the disease, perhaps not an entity,<sup>1</sup> is of virus etiology, although this hypothesis has not been established. Stokes, Kenney and Shaw<sup>7</sup> and Francis and Magill<sup>8</sup> obtained an infectious agent that produced pulmonary lesions in ferrets and mice, but the agent could not be retained. Weir and Horsfall<sup>9</sup> have isolated in the mongoose a filterable agent obtained from patients with acute pneumonitis. Dingle and Finland<sup>1</sup> maintain that the matter of etiology is still unsettled.

The diagnosis of primary atypical pneumonia is difficult and at present rests entirely upon clinical and, in particular, radiologic criteria; and upon the exclusion of other types of bronchopneumonia of established bacteriologic etiology. The recent demonstration of the development of cold agglutinins in primary atypical pneumonia by Peterson, Ham and Finland<sup>10</sup> and Turner<sup>11</sup> may be of further help. Recognizing that another easily detectable condition would be useful in diagnosis, we made a careful and detailed study of the leukocyte formula.

The literature contains references to the blood findings in primary atypical pneumonia, but many of them are cursory remarks and they are not all in agreement. Several<sup>1, 4, 12</sup> indicate that the total leukocyte count is normal but may be elevated as the patient recovers. Some<sup>3, 6, 13, 14</sup> report a leukopenia. Some physicians have been under the impression that lymphocytosis is common, but there are no data in the literature to substantiate this. Goodrich and Bradford<sup>15</sup> report that the neutrophils are normal, as is the total leukocyte count usually, whereas Reimann<sup>4</sup> and Yale and Smetana<sup>5</sup> observed an increase in neutrophils with a normal total count. Middleton<sup>16</sup> has noted a monocytosis of 10 to 18 per cent.

\* Received for publication December 31, 1943.

From the Department of Medicine, University of Wisconsin.

This study was aided in part by a grant from the Wisconsin Alumni Research Foundation.

The present investigation was made upon young adults ill in the Infirmary of the Student Health Service of the University of Wisconsin during the fall, winter and spring of 1942-1943. They comprised University students, civilians, sailors and Waves. The studies are divided into two groups. The first consists of 35 cases in which the diagnosis had already been made and roentgenographic evidence was decisive. As these were, therefore, relatively advanced cases, counts were made on another group of students with respiratory infection as soon as they were admitted to the hospital. Many of these did not develop pneumonia and were dropped, but 15 ultimately developed primary atypical pneumonia, and their blood was also studied thrice weekly or oftener until they left the hospital. Most of the patients had mild or moderately severe disease. No attempt is made here to separate these from the three severe cases, although it was recognized that the latter were more prone to have leukocytosis and marked increases in neutrophiles.

### METHODS

Complete blood counts and hematocrit determinations were made upon each patient at the time he or she was seen, Wintrobe tubes being used for this purpose. Thereafter total and differential leukocyte counts were done thrice weekly or oftener until the patient was discharged as well. The total counts were done in duplicate and the differential count of 500 cells was made from cover slip smears stained with Kingsley's stain. The pipettes and counting chamber were standardized by the U. S. Bureau of Standards.

TABLE I (35)

The Initial Leukocyte Counts of 35 Cases of Primary Atypical Pneumonia  
No significant changes occurred in the basophiles and they are omitted from the table.

W.B.C. Thousands	No.	N. %	No.	L. %	No.	E. %	No.	M. %	No.
2,500-5,000 . . .	1	40-45	1	5-10	3	0-4	25	0-4	
5,001-7,500 . . .	9	46-50	2	11-15	7	5-8	9	5-8	9
7,501-10,000 . . .	14	51-55	2	16-20	14	9-12	1	9-12	14
10,001-12,500 . . .	6	56-60	3	21-25	6			13-16	9
12,501-15,000 . . .	2	61-65	3	26-30	2			17-20	3
15,001-17,500 . . .	2	66-70	14	31-35	2				
17,501-20,000 . . .	1	71-75	6	36-40	1				
		76-80	2						
		81-85	2						
		86-90	1						

N.—Neutrophiles.  
L.—Lymphocytes.

E.—Eosinophiles.  
M.—Monocytes (large mononuclear cells).

*Results.* The results of the first counts of the 35 cases are shown in table 1. These may be summarized as follows: Leukopenia is rare, but a normal leukocyte count, range of 5 to 10,000, is the rule, having occurred in 23 (66 per cent) of the 35. An increase in neutrophiles at the expense of the lymphocytes is also usual. In 25 (71 per cent) the neutrophiles numbered more

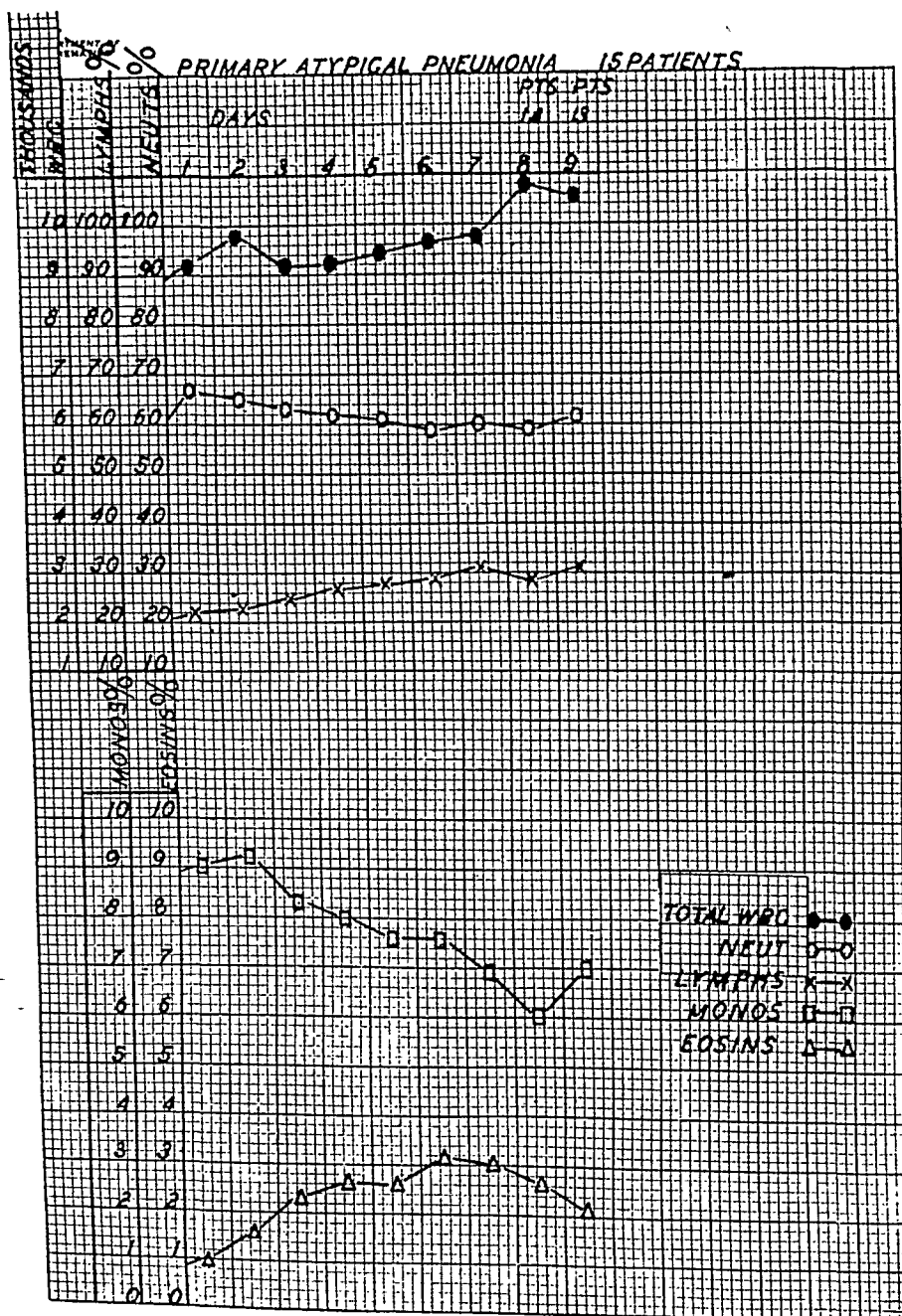


CHART 1. The averages of daily total and differential counts on 15 patients with primary atypical pneumonia. The first counts were done at the very onset of the illness. The basophiles and atypical cells, because of their rarity, are not included.



than 65 per cent of the cells. The lymphocytes were decreased to less than 25 per cent in 30 (86 per cent) of the 35 cases. The eosinophile count was usually normal or subnormal, but in nine (26 per cent) eosinophilia was demonstrated. In 26 (74 per cent) of the cases the monocytes (large mononuclear cells) were increased to more than 8 per cent. There were no significant abnormalities in the basophile count, nor any significant numbers of pathological cells. Hence they were ignored in compiling the table.

The results of the group of 15 cases which were observed from the onset of their disease are shown in table 2.

TABLE II (15)

The Initial Leukocyte Counts of 15 Cases of Primary Atypical Pneumonia  
No significant changes occurred in the basophiles and they are omitted from the table.

W.B.C. Thousands	No.	N.%	No.	L.%	No.	E.%	No.	M.%	No.
2,500-5,000...	2	50-55	1	10-15	2	0-4	15	0-4	0
5,001-7,500...	5	56-60	2	16-20	3	5+		5-8	8
7,501-10,000...	4	61-65	3	21-25	7			9-12	4
10,001-12,500...	1	66-70	6	26-30	1			13-16	2
12,501-15,000...	2	71-75	1	31-35	1			17-20	1
15,001-17,500...		76-80		36-40	1				
17,501-20,000...		81-85	2						
20,001-22,500...	1								

N.—Neutrophiles.

L.—Lymphocytes.

E.—Eosinophiles.

M.—Monocytes (large mononuclear cells).

Analysis of this table shows that nine (60 per cent) of the 15 cases had normal total leukocyte counts and only two had leukopenia. In nine (60 per cent) neutrophiles were increased above normal (above 65 per cent) and in 12 (80 per cent) a lymphopenia was demonstrated. None of this group studied early showed an eosinophilic count above normal. Seven, or almost half, of the patients showed a distinct monocytosis, i.e. above 8 per cent.

The tables reveal that in several respects the findings are the same for the two groups, namely, the normal leukocyte count, neutrophilia, lymphopenia, and monocytosis. The increase in monocytes is less frequent in the early cases, however. Eosinophilia occurs in late cases, but never in early ones. There are no significant differences between the two groups with respect to the frequency of a normal total count, neutrophilia, and lymphopenia, but there is a greater percentage of severe lymphopenias, and marked increases in neutrophiles in the cases of longer standing.

As these patients improved and became afebrile certain changes in the blood formulae were noted which do not appear in the tabulated data. Briefly stated these were as follows: As the patient began to improve and became well (afebrile), there was usually an increase in the total leukocyte count, to above normal levels in half of the cases; a decrease in the neutrophiles and an increase in lymphocytes; a decrease in the eosinophiles,

whether above normal or not, in the older cases, and increases from low levels in the newer cases; and a subsidence of the abnormally high monocyte count in nearly all instances.

### DISCUSSION

In this investigation we have attempted to depict the abnormalities in the leukocyte picture which attend primary atypical pneumonia of undetermined etiology and to correct some erroneous concepts regarding the blood findings. Briefly, one may state that typically at the onset and even after the disease is well established, the leukocyte count is normal; there is an increase in neutrophiles, monocytes, and, in a fourth of the cases, eosinophiles. Coincidentally, a decrease in the lymphocytes is the rule. These findings apply to most cases but not to all. It appears that the finding having most significance as a possible aid in diagnosis is the very appreciable increase in monocytes which occurs in half the early cases and in three-fourths of those more advanced.

We have not done counts on a control series of pneumococcal pneumonias, but it is well known that leukocytosis with an increase in neutrophiles is the usual finding. In influenzal pneumonia and in psittacosis, leukopenia is the rule. In lobar pneumonia a transient monocytosis occasionally accompanies the beginning of resolution.<sup>17</sup> Occasionally a "post-infectious eosinophilia" follows the crisis in lobar pneumonia.<sup>18</sup> Presumably these conditions might occur occasionally in pneumococcal bronchopneumonia too, but apparently they are exceptional.

The findings here reported may prove to be of some aid in the diagnosis of primary atypical pneumonia, but they are not specific enough to justify a categorical statement. They may, however, serve to correct any misconceptions regarding the leukocytic response in primary atypical (virus) pneumonia of undetermined etiology.

### CONCLUSIONS

1. Careful hematologic studies have been made in 50 cases of primary atypical (virus) pneumonia.
2. It was found that the leukocyte count was usually normal, and that the neutrophiles and monocytes increased. A lymphopenia was usually present. In 26 per cent of the cases in which the disease was somewhat advanced, there was eosinophilia at the time the first counts were made, but not in any of the cases where initial counts were made at the very onset of the pneumonia.
3. The leukocyte findings may be of some diagnostic aid but they are not necessarily conclusive.

## BIBLIOGRAPHY

1. DINGLE, J. H., and FINLAND, M.: Virus pneumonias. II, Primary atypical pneumonias of unknown etiology, *New England Jr. Med.*, 1942, ccxxvii, 378.
2. GALLAGHER, J. R.: Broncho-pneumonia in adolescence, *Yale Jr. Biol. and Med.*, 1934, vii, 23. Acute pneumonitis—a report of 87 cases among adolescents, *Yale Jr. Biol. and Med.*, 1941, xiii, 663.
3. BOWEN, A.: Acute influenza pneumonitis, *Am. Jr. Roentgenol.*, 1935, xxxiv, 168.
4. REIMANN, H. A.: An acute infection of the respiratory tract with atypical pneumonia, *Jr. Am. Med. Assoc.*, 1938, cxi, 2377.
5. KNEELAND, Y., JR., and SMETANA, H. F.: Current broncho-pneumonia of unusual character and undetermined etiology, *Bull. Johns Hopkins Hosp.*, 1940, lxxvii, 229.
6. LONGCOPE, W. T.: Bronchopneumonia of unknown etiology (variety X), *Bull. Johns Hopkins Hosp.*, 1940, lxxvii, 268.
7. STOKES, J., JR., KENNEY, A. S., and SHAW, D. R.: A new filtrable agent associated with respiratory infections, *Trans. and Studies Coll. Phys. Philadelphia*, 1939, vi, 329.
8. FRANCIS, T., and MAGILL, T. P.: An unidentified virus producing meningitis and pneumonitis in experimental animals, *Jr. Exper. Med.*, 1938, lxxviii, 147.
9. WEIR, J. M., and HORSFALL, F. L., JR.: The recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose, *Jr. Exper. Med.*, 1940, lxxii, 595.
10. PETERSON, O. L., HAM, J. H., and FINLAND, M.: Cold agglutinins (autohemagglutinins) in primary atypical pneumonia, *Science*, 1943, xcvi, 167.
11. TURNER, J. C.: Development of cold agglutinins in atypical pneumonia, *Nature*, 1943, cli, 419.
12. CAMPBELL, T. A., STRONG, P. S., GRIER, G. S., III, and LUTZ, R. J.: Primary atypical pneumonia. A report of two hundred cases at Fort Eustis, Virginia, *Jr. Am. Med. Assoc.*, 1943, cxxii, 723.
13. CASS, J. W., JR.: The question of influenza and atypical pneumonia, *New England Jr. Med.*, 1936, ccxiv, 187.
14. MAXFIELD, J. R., JR.: Atypical pneumonia with leukopenia, *Texas State Jr. Med.*, 1939, xxxix, 340.
15. GOODRICH, B. E., and BRADFORD, H. A.: The recognition of virus type pneumonia, *Am. Jr. Med. Sci.*, 1942, cciv, 163.
16. MIDDLETON, W. S.: Primary atypical pneumonia, *Proc. Cardiff Med. Soc.*, Session 1942-1943, 1943, pp. 50-57.
17. REIMANN, H. A.: The pneumonias, 1938, W. B. Saunders Co., Philadelphia.
18. PEPPER, O. H. P., and FARLEY, D. L.: Practical hematological diagnosis, 1933, W. B. Saunders Co., Philadelphia.

## THE USE OF BENZEDRINE SULFATE IN OBESITY \*

By FREDERICK K. ALBRECHT, P. A. Surgeon, U. S. Public Health Service.  
*Baltimore, Maryland*

RECENT studies have led to the conclusion that a continuous gain in weight resulting in obesity is caused by eating more than is needed for growth, maintenance and energy requirements. In the normal person, the appetite is satisfied at a point where nourishment is adequate and the weight becomes stabilized. In the obese person the appetite is not satisfied on such a level, and an excessive amount of food is ingested. There is a prevalent belief among some that persons occasionally gain weight even though they do not overeat, and that others do not lose weight when they are underfed. Recent studies<sup>1</sup> lend overwhelming support to the statement that obesity is not caused by lessened expenditure of energy in the basal state. It has been shown by Newburgh that an obese person produces more heat than a normal person of corresponding age, height, and sex. Although both produce the same number of calories per square meter of body surface per unit of time, the obese person has a larger surface area, and therefore the total heat produced by the obese person in the basal state exceeds the total heat produced by the normal person. Strouse, Wang, and Dye<sup>2</sup> have compared the basal metabolic rates of normal persons with those both underweight and overweight. They concluded there was practically no difference. According to Newburgh,<sup>3</sup> the few obese persons whose metabolic rate is low enough to be definitely pathological will be found to be suffering from some disease in which adiposity is a complication or an unrelated accompaniment and not the primary abnormality. Many painstaking studies<sup>4</sup> have demonstrated that the specific dynamic effect is normal in obese persons. For a time it was believed by many endocrinologists that hypofunction of the pituitary, the thyroid, or the gonads offered an adequate explanation of the development of adiposity. Further study has shown this is not the case.<sup>5, 6</sup> No internal secretion is capable of so changing the metabolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow. No one has demonstrated low blood sugars in patients whose chief complaint was obesity. On the other hand, hyperglycemia may commonly be encountered.

*The Use of Benzedrine Sulfate as an Adjunct in the Management of Obesity.* The problem frequently arises as to how the appetite can be controlled so that a prescribed reducing diet will be adhered to. Lesses and Myerson<sup>17</sup> found that when benzedrine sulfate was administered to various psychotic adult patients, there frequently resulted a decrease in the appetite, a

\* Received for publication January 31, 1944.

disappearance of the feeling of fatigue, and a beneficial influence on the state of the mind. With the decrease in appetite there followed voluntary restriction of diet, and weight loss resulted in many patients. On the basis of this work, Kunstadter<sup>7</sup> was induced to treat obesity in children using benzedrine. He administered the drug to 30 obese children between 2½ and 16 years of age who had failed to lose weight on prescribed diets. Many had also received thyroid extract. The drug was given either twice or three times daily, before breakfast and lunch, and after school if a third dose was considered necessary. Many of the children took as much of the drug as usually prescribed for adults without any untoward symptoms. In his series, the majority of patients received a daily dose of from 10 to 30 mg. The average weekly loss of weight of 26 patients who received continuous treatment for over two weeks was 0.831 pounds. There was little or no variation in the basal metabolic rate while under treatment.

Just how benzedrine acts to reduce weight is not entirely clear. In doses of 10 to 30 mg., orally administered, it delays the rate of evacuation of the stomach.<sup>8, 9, 10, 11, 12</sup> The drug apparently relaxes the stomach and increases the tone of the pylorus. Benzedrine has been reported to relax esophageal spasm.<sup>13</sup> Gastric acidity tends to be increased without an increase in volume.<sup>14</sup> The drug has no marked effect upon the small intestine (20–30 mg.) and its effect on the colon is apparently variable, though it has been claimed to be of value in colonic spasm. A study of the available literature reveals considerable difference of opinion concerning the action of benzedrine upon the gastrointestinal tract, and both clinical and animal experimentation has furnished results not entirely consistent. The action of benzedrine upon the small bowel is both uncertain and unpredictable. The cardiovascular response in man to benzedrine is extremely variable. As a rule dosages up to 15 mg. have but little response as to pressor effects if taken orally. Only oral dosages of 30 mg. or more induce any significant increases in tension, and in some cases a paradoxical fall in blood pressure has been reported. It is thus seen that the response to oral administration is unpredictable. Hypertensive patients tend to show a fall in blood pressure when in poor health, whereas hypotensive patients may show an increase in blood pressure.

According to the literature, arrhythmias of different types may occasionally occur including auricular and ventricular extrasystoles, paroxysmal tachycardia, bradycardia, and heart block. The following vascular actions have been reported: flushing, pallor, urticaria and sweating. Patients receiving the drug may complain of dryness of the mouth, palpitation, flatulence, anorexia, nausea, abdominal cramps, diarrhea, or constipation. In the author's experience with more than 400 cases, the principal symptoms reported by the patients are: dryness of the mouth, headache, palpitation, euphoria, coldness of the hands and feet, insomnia if the drug is taken late in the afternoon, and loss of appetite. The inability of benzedrine to ele-

vate the blood sugar has been confirmed by several workers. The rise in the basal metabolic rate following benzedrine administration is negligible, inconstant, and not significant. The few instances in which it has been reported have been attributed to the increased psychomotor activity induced by the drug. Continued administration of the drug has no effect upon the blood picture. The literature contains many references to the value of the drug in helping obese patients adhere to a low calorie diet for reducing purposes.<sup>15, 16, 17, 18, 19</sup> There have been a few reports of a gain in weight following the use of the drug.<sup>20, 21</sup> In cases in which there has been demonstrated a decrease in weight, it has been attributable to increased activity, increased metabolic rate (*this is dubious*), anorexia due to inhibition of gastric tone, and elevation of mood.<sup>22, 23</sup> Bruch<sup>24</sup> suggested that the decrease in appetite and loss of body weight may be due in part to the effect of the drug upon the hypothalamus.

*Clinical Results in 300 Cases.* In this series of cases reported, 300 patients were studied, 76 males and 224 females. The ages ranged from 21 to 53 years and their weights before treatment was instituted varied from 138 pounds to 310 pounds. The dosage of the drug varied from 10 mg. daily to 30 mg. daily in divided doses. It was never prescribed after 4 p.m. except in a few instances in which the patient was employed at night. The duration of treatment varied, covering periods from two weeks to two months, although in almost all cases the patients were followed for from two to eight months. This follow-up study was greatly facilitated by the fact that many of the patients were hospital personnel such as cooks, maids, office workers and nurses and consequently were seen almost daily in the author's rounds of the hospital. Many of the patients were cooks or others who worked around food and who admitted eating liberally between meals. Many of the office workers, especially the females, admitted almost daily drinking of from one to three coca-colas and an occasional candy bar between meals.

In all cases, treatment was started without any dietary restrictions being imposed, the patient thus eating as his caprice or appetite dictated. When an optimal weight for the individual patient had been reached, the patient was advised to go on a 900 or 1,000 calorie diet. In some cases in which the patient was doing hard manual labor a more liberal diet was allowed. The average weekly weight loss while taking the drug was 4.24 pounds for the males and 3.94 for the females. The greatest individual loss of weight for any one week was 13.5 pounds. The smallest weight loss per week by any one patient was 0.5 pound. This patient admitted drinking large quantities of beer daily. The greatest individual loss of weight was 52 pounds over a period of two months. Twenty-four per cent of the patients noted no apparent loss of weight during the first week of treatment but reported their maximal weekly weight loss as occurring during the second week of treatment. All patients with the exception of one lost weight while taking the drug.

TABLE I  
Symptoms Following the Use of Benzedrine

Loss of appetite.....	88%
Little or no change in appetite.....	10%
Increased appetite.....	2%
Psychomotor activity	
Increased.....	48%
No change.....	44%
Decreased.....	8%
Palpitation (all females).....	12%
Headache.....	32%
Xerostomia.....	56%
Anxiety.....	14%
Euphoria.....	22%
Insomnia.....	4%
Urinary retention.....	0.33%
Coldness of extremities.....	2%

In the 12 per cent of cases reporting *palpitation*, it was severe enough in 4 per cent to cause the drug to be discontinued; in the remainder of the patients, it was controlled by the administration of 1 grain of luminal with each dose of the drug. *Anxiety* was present in 14 per cent of the patients. It was not constant, and histories revealed it to have been present to some extent in 8 per cent of cases before taking the drug. *Euphoria* was noted in those who were black coffee drinkers and who followed the morning dose of benzedrine with two or three cups of black coffee. *Insomnia* was directly traceable to the drug being taken late in the afternoon, contrary to medical advice. *Xerostomia* or dryness of the mouth was relieved by chewing gum.

Many patients, especially women, noted no actual weight loss for the first two weeks they were taking benzedrine, yet they were greatly surprised to find that they were able to wear clothes, nurse's uniforms, etc., which they had outgrown years before. In several of these cases, actual measurements revealed a loss of from two to three inches in the waist and hip measurements. Questioning revealed many had been drinking large quantities of water as a result of the induced xerostomia. Chewing gum relieved this immediately, and actual weight loss soon followed. Urinary retention was reported in one case. This patient, an astute observer, noted that when he stopped taking the drug, all signs of retention disappeared only to return on resumption of the drug. The author has been unable to find any other case reported with such symptoms following benzedrine therapy in the literature. This same patient was known to have a moderate arterial hypotension before taking the drug. He felt much better while taking benzedrine, and examination revealed the existence of a moderate pressor response amounting to between 20 and 30 millimeters of mercury systolic pressure, 10 to 14 millimeters of mercury diastolic pressure. Two cases developed a sudden rise in blood pressure which resulted in the drug being discontinued. In one patient it rose from 110 mm. Hg systolic and 80 mm. diastolic to 150 mm. systolic

and 110 mm. diastolic; in another it rose from 160 mm. systolic and 110 mm. diastolic to 200 mm. systolic and 160 mm. diastolic.

One group of 20 patients, all women, was put on the drug for two months and without their knowledge, placebos, having the same size, shape, and taste as benzedrine (Placebo No. 10—Smith, Kline and French) were substituted during the third month of therapy. In 14 of these patients, a loss of weight was seen to continue into the third month, only at a lesser rate than before. They all noted that they had no desire to partake of soft drinks or candy bars between meals. The remaining six patients noted a gradual resumption of their former appetites and they soon fell into their former habit of "nibbling" between meals. A subsequent follow-up after 20 months on the 14 patients mentioned heretofore reveals that 11 of them have been able to curb their appetite and adhere to diets prescribed for them. They have not gained any weight and are not taking any benzedrine.

Additional follow-up studies on 174 patients since 1941, of whom 52 were males and 122 females, reveals that 44 males and only 32 females have been able to stay on their diets and maintain their optimal weight. Many of the female patients bitterly resented having the drug discontinued, and have resumed their former eating habits which has resulted in almost all cases in an increase of weight.

Blood pressures were carefully checked at the beginning of the treatment as well as frequently during the course of therapy and at its discontinuance. Approximately 30 per cent of patients showed an average rise of 8 mm. of mercury systolic pressure. Three per cent of patients showed an average rise of between 10 and 15 mm. of mercury systolic pressure. Twenty-six per cent of patients showed a gradual decrease in blood pressure as they lost weight. Approximately 40 per cent of cases showed little or no change in the blood pressure. It has been observed in the literature,<sup>19, 24</sup> that upon protracted administration of benzedrine, a tolerance to the pressor effect frequently occurs after a few days.

*Management of Treatment.* Patients are started on 5-mg. of benzedrine sulfate twice daily, the drug to be given one-half to one hour before breakfast and the noon meal. If the patient works at night the dose is adjusted accordingly. In those who eat a very light breakfast and who eat their evening meal fairly early, the drug is given one hour before the noon meal and at 4 p.m. In not a few cases the author has given the drug as late as 6 p.m. without any insomnia resulting. After a few days the dosage can be increased to 10 mg., especially if the patient reports no loss of appetite. It is not uncommon for no loss of weight to be apparent for 12 days following the initiation of therapy. Persistence will usually be rewarded by a rapid loss of weight for a few weeks when it will taper off to a more gradual reduction. Dosage is strictly an individual matter and in many cases 10 mg. has shown an effect comparable to 30 or even 40 mg. daily. Special diets can be started after a few weeks. The author uses those of Newburgh.<sup>3</sup>



*Contraindications to Benzedrine Sulfate Therapy.* The contraindications to benzedrine sulfate are: (1) a hypersensitivity to epinephrine-like compounds, (2) coronary or other cardiac conditions in which vasoconstrictors are contraindicated, (3) excitability, and (4) insomnia.

### CONCLUSIONS

Benzedrine sulfate appears to be a valuable adjunct in the management of obesity under the advice and supervision of a physician. Nearly all patients taking the drug lose their propensity for eating between meals and before going to bed. Diets alone, unless they are very low in calories, produce such slow results that the average patient loses heart and does not cooperate in the treatment. Given benzedrine, they see the actual results as weight is lost where most noticeable; their friends are quick to see the result and comment about it which tends to make the patient very happy and enthusiastic in his treatment. They can be put on a diet varying in calories from 450 to 1,500 with an excellent chance that they will stay on it after the drug is discontinued. In some respects the drug is too effective an adjunct to the restricted diet and many patients will seek its continued use as a "crutch." It is apparent that here is an easy and rapid way to lose weight, and, under the guidance and supervision of a physician mindful of the contraindications to benzedrine therapy, relatively free from any ill effects. Obese patients taking the drug lose their uncontrollable desire to eat at various times of the day and are more easily filled at meal time.

Benzedrine should not be considered a panacea, but rather an effective adjunct in the management of selected cases of obesity. The author has seen no case of habituation for the drug either in this series or in his series of 100 cases of seasickness.<sup>25</sup> The weight loss is not permanent; it is transient in the great majority of instances and returns when the drug is discontinued unless the patient remains on his special diet. During the time the drug is being prescribed, however, the patient is able to adjust his abnormal appetite at a new level and may be able to maintain his new weight level for a considerable time after the drug is discontinued.

### BIBLIOGRAPHY

1. GRAFE, E.: *Metabolic diseases and their treatment*, 1933, Lea and Febiger, Philadelphia.
2. STROUSE, S., WANG, C. C., and DYE, M.: *Studies on the metabolism of obesity*, Arch. Int. Med., 1924, xxxiv, 275.
3. NEWBURGH, L. H.: *Obesity*, Arch. Int. Med., 1943, lxxi, 1033-1096.
4. STRANG, J. M., and McCLUGAGE, H. B.: *The specific dynamic action of food in abnormal states of nutrition*, Am. Jr. Med. Sci., 1931, clxxxii, 49.
5. GREENE, J. A.: *Clinical study of the etiology of obesity*, Ann. Int. Med., 1939, xii, 1797.
6. BRUCH, H.: *Obesity in childhood: 1. Physical growth and development in obese children*, Am. Jr. Dis. Child., 1939, lviii, 457.
7. KUNSTADTER, R. H.: *Experience with benzedrine sulfate in the management of obesity in children*, Jr. Pediat., 1940, xvii, 490.

8. RITVO, M.: Drugs as an aid in roentgen examination of the gastrointestinal tract, *Am. Jr. Roentgenol.*, 1936, xxxvi, 868.
9. VAN LIERE, E. J., and SLEETH, C. K.: The effect of benzedrine sulfate on the emptying time of the stomach, *Jr. Pharmacol. and Exper. Therap.*, 1938, lxii, 111.
10. ROSENBERG, D. H., ARENS, R. A., MARCIS, P., and NOCHELES, H.: Benzedrine sulfate: Its limitations in the treatment of the spastic colon and a pharmacologic study of its effect on the gastrointestinal tract, *Jr. Am. Med. Assoc.*, 1938, cx, 1994.
11. PEOPLES, S. A., and GUTTMANN, E.: Hypertension produced with benzedrine, *Lancet*, 1936, i, 1107.
12. BEYER, K. H., and MEEK, W. J.: Effect of benzedrine on gastric emptying and intestinal activity, *Arch. Int. Med.*, 1939, lxiii, 752.
13. SCHMIDT, H. W.: Diffuse spasm of the lower half of the esophagus, *Am. Jr. Digest. Dis.*, 1939, vi, 693.
14. MYERSON, A., RINKEL, M., and DAMESHEK, W.: The anatomic pharmacology of the gastric juice, *New England Jr. Med.*, 1936, ccxv, 1005.
15. ROSENTHAL, G., and SOLOMON, H. A.: Benzedrine sulfate in obesity, *Endocrinology*, 1940, xxvi, 807.
16. FULTON, G., and HUMPHREY, E. C.: The management of obesity, *Kentucky Med. Jr.*, 1939, xxxvii, 110.
17. LESSES, M. F., and MYERSON, A.: Benzedrine sulfate as an aid in the treatment of obesity, *New England Jr. Med.*, 1938, ccviii, 119.
18. MYERSON, A., LOMAN, J., and DAMESHEK, W.: Physiologic effects of benzedrine and its relationship to other drugs affecting the autonomic nervous system, *Am. Jr. Med. Sci.*, 1936, cxcii.
19. ULRICH, H.: Narcolepsy and its treatment with benzedrine sulfate, *New England Jr. Med.*, 1937, ccxvii, 696.
20. BAKER, R. W.: Recognition of orthostatic hypotension, *Proc. Staff Meet. Mayo Clin.*, 1938, xiii, 169.
21. DUB, L. A., and LURIE, L. A.: Use of benzedrine in the depressed phase of the psychotic state, *Ohio State Med. Jr.*, 1939, xxv, 39.
22. NATHANSON, M. H.: The central action of benzedrine, *Jr. Am. Med. Assoc.*, 1937, cviii, 579.
23. BEYER, K. H.: The effect of benzedrine sulfate on metabolism and the cardiovascular system in man, *Jr. Pharmacol. and Exper. Therap.*, 1939, lxvi, 318.
24. BRUCH, H.: Obesity in childhood, *Am. Jr. Dis. Child.*, 1940, lix, 739.
25. ALBRECHT, F. K.: Therapeutic evaluation of benzedrine sulfate in the treatment of seasickness: Results in 100 cases, *Med. Clin. N. Am.*, 1943, 1652-1658.

# MIGRAINE HEADACHE: SOME CLINICAL OBSERVATIONS ON THE VASCULAR MECHANISM AND ITS CONTROL \*

By MILES ATKINSON, M.D., F.R.C.S.(ENG.), *New York, N. Y.*

IN a previous paper, it was shown that headache possessing all the characteristics of migraine is not uncommonly associated with Menière's syndrome,<sup>1</sup> a fact which was pointed out originally by Menière himself. Sometimes the migraine attacks subside some years before the onset of the Menière attacks, sometimes they are replaced by the Menière attacks, and sometimes the two are present together. It was stated that, in the opinion of the writer, the vascular mechanism producing the two syndromes is identical, and the observations on which this opinion was based were discussed. It was also shown that the treatment directed towards relief of vertigo relieved at the same time the attacks of headache in a large proportion of cases.

In view of these findings, it seemed appropriate to adopt the same procedure of classification and treatment for cases of uncomplicated migraine as had been used for cases of uncomplicated Menière's syndrome in order to determine how far the hypothesis of an identical mechanism was valid, and to what extent identical treatment would prove beneficial. This paper reports the results of such an investigation.

*The Material.* Twenty-one cases of uncomplicated migraine have been investigated and followed over periods varying from six months as a minimum to two years as a maximum. The criteria adopted for diagnosis have been that paroxysms of unilateral headache associated with nausea or vomiting shall have occurred since adolescence or early adult life, and shall have been severe enough to be incapacitating, at least at times. The association of visual disturbances (nine cases), a hereditary factor (12 cases) or relief by ergotamine tartrate (10 cases) has been regarded as confirmatory evidence in accordance with common current practice. In no case was hypertension present.

*The Method of Classification.* To make this clear, it is necessary very briefly to recapitulate previous work. Cases of Menière's syndrome, it has been shown, can be divided into two groups by determining their response to an intradermal test for histamine sensitivity, and the validity of this grouping has been established by clinical experiment and therapeutic response.<sup>2, 3</sup> Further, it has been shown that characteristic migraine occurs in both groups and is improved, or in some cases abolished completely, by the treatment appropriate to the group.<sup>1</sup>

\* Received for publication November 10, 1943.

Paper read by title at the Clinical Research Meeting of the New York Academy of Medicine, May 27, 1943.

The same procedure was adopted in these 21 cases of uncomplicated migraine. An intradermal test with histamine was performed in the manner and judged by the criteria already described in previous papers. The upshot of this investigation was that no case gave a positive response. This means, if the writer's views about the significance of the test as regards the underlying vascular mechanism are accepted, that no case owned a primary vasodilator mechanism, that every one of the 21 cases of typical uncomplicated migraine owned a primary vasoconstrictor mechanism.

This finding was unexpected. The writer's figures show that, of 22 cases of typical migraine associated with Menière's syndrome, 10 belonged to the primary vasodilator group. If the same proportion of primary vasodilator cases occurred in uncomplicated migraine, at least five out of

TABLE I  
21 Cases of Vasospastic Migraine Headache Treated with Nicotinic Acid

Case No.	Date First Seen	Sex	Age of Onset	Family History	Scoloma etc.	Ergot. Tart.	Frequency and Severity		Results			
							Before Tr.	After Tr.	Rel.	Gt. Impt.	Mod. Impt.	Fail.
1	Dec. '42	F	24	+	+	Relief	4/7++++	4/28++			+	
2	Dec. '42	F	15	+	0	Not used	1/28++	0/28	+			
3	Dec. '42	F	10	+	+	No relief	7/7++++	3/7++			+	
4	Nov. '42	M	34	+	+	Relief	1/7+++	1/7+++				+
5	Nov. '42	M	35	+	0	Relief	7/7++++	2/7+		+		
6	Nov. '42	M	25	?	0	No relief	2/28++++	1/3 mos. +		+		
7	Oct. '42	F	10	+	+	Not used	3/28+++	3/28+++				+
8	Oct. '42	F	12	0	+	Relief	1/7+++	1/7+++				+
9	Oct. '42	F	34	+	0	No relief	2/28++	0/28	+			
10	Oct. '42	M	18	0	0	Relief	2/28+++	1/28+		+		
11	Sept. '42	F	17	0	0	Relief	1/28+++	1/2 mos. +			+	

++++ = very severe. +++ = severe. ++ = moderate. + = mild. Rel. = relief. Impt. = improvement. Fail. = failure.

In the column headed "Frequency and Severity," the numerator of each fraction indicates the average number of attacks in a given interval of time, and the denominator, the length of the interval in days, unless otherwise indicated. The severity is indicated by + marks.

TABLE I—Continued

Case No.	Date First Seen	Sex	Age of Onset	Family History	Scoloma etc.	Ergot. Tart.	Frequency and Severity		Results			
							Before Tr.	After Tr.	Rel.	Gt. Impt.	Mod. Impt.	Fail.
12	Sept. '42	M	22	+	+	No relief	3/7++++	1/2 mos. +		+		
13	Sept. '42	F	25	+	0	Relief	2/28++++	1/3 mos. +		+		
14	Sept. '42	F	30	0	+	Relief	3/7+++	3/28+			+	
15	Sept. '42	F	10	0	0	Not used	6/28++++	2/28++			+	
16	June '42	F	19	+	+	Not used	2/28+++	1/3 mos. +		+		
17	June '42	F	21	+	0	Relief	3/7+++	1/28+		+		
18	June '42	F	13	+	0	No relief	1/7+++	1/7+++				+
19	June '42	M	31	0	0	Relief	3/28+++	Occas. +		+		
20	May '41	F	29	0	+	Not used	4/7++++	1/3 mos. +		+		
21	Mar. '41	F	10	0	0	Not used	2/28+++	Occas. +		+		

these 21 cases should have given a positive response to the histamine test. Not one did. The implications of this observation will be discussed later.

*Method of Treatment.* Since all the cases belonged to the same group, the primary vasoconstrictor, the only form of treatment used was that which had been found satisfactory for the same group in Menière's syndrome, that is to say, nicotinic acid used for its vasodilator action. The reasons prompting the choice of this substance as a suitable vasodilator have been fully discussed elsewhere.<sup>1, 2, 3</sup> There also the method and routine of administration found most satisfactory have been fully described.

Briefly, the routine is to give first an intramuscular injection of 25 to 35 mg. in order to determine by the extent of the flush reaction the individual tolerance of the patient, which can vary within wide limits. Estimating dosage from that, a series of six or eight intravenous injections is given, starting with 20 to 30 mg. and rising by daily increments of 5 mg. to 50 mg. or such lower limit of tolerance as may be determined. A higher dose than 50 mg. is seldom required, and in general the dosage necessary for migraine patients is lower than that for Menière patients. This may be because the vascular tree of the migraine sufferer is more resilient than that of the

Menière patient. Indeed the very fact of having migraine is evidence of a capacity for vasodilation.

After the course of intravenous injections, the patient is taught to give himself intramuscular injections of such a strength (25 to 50 mg.) and at such intervals (daily, three weekly) as experience and the severity of the symptoms indicate.\* At the same time tablets (50 to 150 mg. daily) are given. After a period which is determined by the response to treatment, the patient is weaned from injections and kept on a maintenance dose by mouth.

The reason for insisting upon injection therapy in the beginning is that it has been established by experience that many patients who have not responded to nicotinic acid by mouth have responded well when the method of administration has been changed to parenteral. Presumably some people absorb nicotinic acid from the stomach poorly or not at all. In four cases only, none of them very severe, have tablets alone proved sufficient from the beginning.

In addition to medication, a high protein-low carbohydrate diet is recommended, and advice given as to rest and exercise and the beneficial effects on the vasomotor system of alternating warm and cool showers. Smoking is discountenanced and when possible stopped, on the grounds that migraine is a peripheral vascular disorder.

*Results.* The results are shown in the accompanying table. All patients except three have been seen or have answered a questionnaire within a month of the writing of this report. The three who did not reply have been adjudged on the record of their last visit.

1. *Complete relief* from headaches has been obtained in two cases only, and over periods of six months and four months (headaches averaged previously two a month and one a month respectively, and were only of moderate intensity). This is quite evidently too short a time upon which to base a final estimate. Indeed, it is with some misgiving that this group has been allowed at all, for cure is not a result which can be envisaged in migraine. Because of the unchangeable constitutional background of the condition, the most that can be hoped for is to prevent the mechanism from going into action so frequently and so powerfully and thus to achieve a measure of relief. That this measure can, however, be a considerable one will be seen in considering the next group.

2. *Improvement* has been obtained in 15 cases, and has been classified by the patients themselves as great in 10 cases and moderate in five. Eight suffered frequent very severe and usually incapacitating headaches, the other seven less frequent, less severe and seldom incapacitating headache.

(a) *Great improvement* has been obtained in four cases of great severity and in six cases of moderate severity.

Two examples of the very severe group may be briefly mentioned. Case

\* The injectable nicotinic acid used in this investigation has been Nicamin (Abbott), generous supplies of which have been provided by Abbott Laboratories, Inc.

20, a woman who had at least one incapacitating headache a week and two or three others less severe but enough to make work a difficulty, now has an occasional mild headache every two to three months. Case 12, a lawyer, had two or three times a month headache of such severity that he would beat his head against the wall, as well as numerous less severe headaches of which he took little account. After nine months of treatment he had no headaches of the severe type and only rarely a headache at all, as long as he took tablets regularly and an occasional injection. Only if, as has occurred once or twice, he commits some gross indiscretion of living, does he have anything in the nature of a severe headache. But, as he says himself, "You can't reasonably expect the stuff to prevent a hangover!"

Of the moderately severe group, case 19 has particular interest. He is a male executive who used to suffer about three fairly severe headaches a month which had been ascribed to allergy, on account of which certain foods (milk, cheese, tomatoes) had been banned. On tablets alone he has been so much improved that he gets no more than an occasional mild headache, in fact claims that he is "cured." Moreover, he finds that now he can take with impunity the foods which formerly he had to avoid.

(b) *Moderate improvement* has been effected in four cases of great severity, in one of moderate severity. Two of the four cases of great severity were in women who had daily headaches, whose lives were a misery, and who had come to rely largely on codein for surcease from their sufferings. One had been subjected to many treatments, appropriate and inappropriate. Both are now free of codein, and their headaches, though still frequent, are from the testimony of a daily record kept by themselves, less frequent and less severe, and steadily diminishing.

3. *Failure.* Four cases have been complete failures. No alleviation of symptoms has resulted, though the régime of treatment was faithfully followed. All are in the moderately severe class.

## DISCUSSION

The object of this paper is not to add yet another to the long list of migraine "cures," nor to boost nicotinic acid as the final answer to the migraine sufferer's prayers. Its object is rather to discuss the mechanism and classification of migraine, and a rationale of treatment which seems to offer hope.

### 1. *Mechanism and Classification*

(a) Wolff and his co-workers have demonstrated<sup>4</sup> that at least in a portion of cases the basic mechanism of the attack is primary vasospasm which produces the visual disturbances, and that the headache, though the more prominent symptom, is in fact only a manifestation of the secondary or reactionary vasodilation. Substantiation of this view of the mechanism is to be found in the following observation. One of the patients (No. 3)

included in this report started to develop at 7:10 p.m. a visual disturbance which, on the basis of experience, presaged a severe and incapacitating headache. It was possible to give her within 20 minutes of the onset an intravenous injection of 75 mg. of nicotinic acid. The flush reaction even from this large dose was very mild. In five minutes the scotoma began to diminish and in 30 minutes it had disappeared. She went to bed and to sleep, without narcotic, and woke next morning with a slight headache which did not prevent her work as a writer. On other similar occasions she had experienced a much longer period of scotoma and an entirely incapacitating headache on the following day.

(b) Other observers maintain that the manifestations of migraine are to be ascribed to an exudative diathesis or allergy, that is to say, in vascular terms, to a primary vasodilator mechanism. There is abundant clinical evidence to support this view of the causation of migraine attacks in at least a proportion of the cases, though the size of that proportion tends to vary with the degree of enthusiasm of the proponent.

Each school of thought maintains its own view to the exclusion of the other—the vasospastic school scoffs at allergy, the allergists at vasospasm. But what if both are right? What if the syndrome known as migraine may be produced by two different mechanisms? What if both these mechanisms are accepted? There is good evidence for each. In that case, there is admitted for the migraine syndrome the identical dual mechanism which the writer has shown to be valid for Menière's syndrome.

These two groups can be differentiated by means of the histamine skin test, at least in patients exhibiting the features of Menière's syndrome.\* If the basic mechanism of migraine and of Menière's syndrome is the same, it would be expected that the histamine skin test would be equally effective in both conditions. Yet, as has been said, in this series of 21 cases none showed a positive response to histamine when at least five would have been expected to do so if the proportions of the two groups were the same in the two conditions. Why the discrepancy?

The reason may not be so far to seek. Obviously the numbers involved in this investigation are too small to warrant the drawing of any far-reaching conclusions. Nevertheless, the fact that not one of these 21 cases of uncomplicated migraine belonged to the primary vasodilator group, whereas in cases associated with Menière manifestations almost half of the total (10 out of 22) belonged to this group, suggests that where a primary vasodilator mechanism is at work its effects are more widespread than those of a primary vasoconstrictor mechanism. Whereas vasospasm tends to be a local phenomenon and, therefore, to present symptoms confined to one locality, in the

\* It must not be assumed from what has been said that the histamine skin test serves as a satisfactory general test for protein sensitivity, for it does not. Many patients with known allergies, seasonal hay fever for instance, have been tested and found to give a normal response to histamine. The biochemical implications of the test are not as yet clear; its practical value, however, has been proved.



case of migraine to the region of the calcarine fissure, vasodilation on the other hand tends to be a more widespread phenomenon and might, therefore, be expected to affect other areas as well as the calcarine and even other adjacent organs as well as the brain, such as the labyrinth. It is commonly claimed that this is the explanation for the sensory, motor, aphasic and ophthalmoplegic phenomena that are occasionally associated with migraine. It would be of more than passing interest to determine the reaction of such cases to histamine. The opportunity to do so unfortunately has not so far presented itself to the writer.

However that may be, it would seem, as far as the limited observations contained in this paper go, that classical uncomplicated migraine is usually if not always a primary vasospastic phenomenon confined to, or at least mainly manifested in, the calcarine area and followed by a secondary vasodilation of intra- or extradural vessels which produce the headache.

Put another way, the clinical evidence presented here is against the common concept of a primary vasodilator mechanism as exemplified by allergy as a causative factor in uncomplicated migraine. Theoretically, this is what might be expected, since it is difficult to conceive of an exudative process as being sharply localized. As Wilson says "If oedema really causes the visual symptoms it should cause much more at the same time."<sup>7</sup> Perhaps it does.

It looks as if once again similarity of symptoms has led to the grouping under one name of two or more pathologically diverse conditions. Periodic headache is not necessarily migraine, nor is it due to any single cause. It may on the contrary be the result of such diverse conditions as vasospasm, allergy, exudative diathesis or endocrine disturbance. Unfortunately, migraine is too often used loosely to cover all these and others too. Hence, much of the confusion and the multitude of "curses."

2. *The Rationale of Treatment with Nicotinic Acid.* This refers only to the primary vasoconstrictor group, in which the postulated mechanism is a primary vasospasm which produces scotoma, a secondary vasodilation which produces headache. The rationale for the use of nicotinic acid is that, by attacking the primary mechanism with a vasodilator drug, the onset of headache may be prevented, that even in time the mechanism may be overcome. This seems a more rational procedure than to wait for the secondary vasodilation to produce the headache, and then to treat that with vasoconstrictor drugs such as ergotamine tartrate which, whatever their immediate effect upon the headache may be, must and do tend to increase and perpetuate the underlying vasoconstrictor mechanism. It was this same reasoning which actuated Engle and Evanson in their use of potassium thiocyanate,<sup>5</sup> another vasodilator drug.

That the reasoning is sound is indicated by the results obtained both with potassium thiocyanate<sup>5, 6</sup> and with nicotinic acid as reported here. Both are vasodilators and both are at least partially effective in a large proportion of cases. Nicotinic acid has this advantage over potassium thiocyanate, that

it is less potentially dangerous. It has the disadvantage that to obtain satisfactory results, parenteral therapy is usually necessary. Neither, however, has yet been used enough to decide between them. The use of both is empirical in the sense that they attack not the basic cause of the vasospasm, which remains conjectural, but only the effect. Nevertheless, in the present state of knowledge, both drugs would seem to merit more extensive trial.

### SUMMARY

1. The results of the treatment of 21 cases of vasospastic migraine with nicotinic acid are described.

2. The mechanism of the migraine syndrome and its possible grouping is discussed, with observations on the results of the histamine skin test in this condition.

3. The rationale for the treatment of migraine with nicotinic acid and with potassium thiocyanate is considered.

### BIBLIOGRAPHY

1. ATKINSON, M.: Menière's syndrome and migraine; observations on a common causal relationship, *Ann. Int. Med.*, 1943, xviii, 797.
2. ATKINSON, M.: Observations on the etiology and treatment of Menière's syndrome, *Jr. Am. Med. Assoc.*, 1941, cxvi, 1753.
3. ATKINSON, M.: Diagnosis and treatment of Menière's syndrome, *Arch. Otolaryngol.*, 1943, xxxvii, 40.
4. WOLFF, H. G., CAHAN, A. M., and SCHUMACHER, G. D.: Studies of migraine: The contrast of vascular mechanism in headache and preheadache phenomena, *Proc. Am. Neurol. Assoc.*, 66th Annual Meeting, June 6-9, 1940.
5. ENGLE, D. E., and EVANSON, C. O.: Effect of potassium thiocyanate on occurrence of migraine, *Am. Jr. Med. Sci.*, 1942, cciv, 625.
6. HINES, E. A., JR., and EATON, L. M.: Potassium thiocyanate in the treatment of migraine: a preliminary report, *Proc. Staff Meet. Mayo Clinic.*, 1942, xvi, 254.
7. WILSON, S. A. KINNIER: *Neurology*, 1941, The Williams & Wilkins Company, Baltimore, vol. II, p. 1587.

## SPONTANEOUS MEDIASTINAL EMPHYSEMA \*

By HENRY MILLER, Captain, Medical Corps, A. U. S.

MEDIASTINAL emphysema is not a rare condition and has been recognized clinically for more than a century. McGuire and Bean,<sup>1</sup> in a comprehensive review of the literature prior to 1939, attribute to Laennec the original description of curious grating sounds and bubbling râles during respiration as diagnostic signs of subpleural and interlobar emphysema of the lungs. Hamman<sup>2</sup> points out that even before Laennec physicians had recognized the occurrence of interstitial emphysema of the lung by noticing subcutaneous emphysema about the neck following trauma to the chest and after overdistention of the lungs by violent effort. Pneumomediastinum has been reported secondary to operations on the throat, thyroid, esophagus, lung, and abdomen; following traumatic injury of thorax, rupture of an abdominal viscus and perforation of the esophagus by foreign bodies. It has also been recorded as a complication of artificial pneumothorax, pneumoperitoneum, intubation in children, difficult childbirth, severe exertion and in such diseases as influenzal bronchopneumonia, croup, pertussis, diphtheria, bronchial asthma, and pulmonary tuberculosis.

Müller,<sup>3</sup> in 1888, described certain characteristic physical signs indicative of pneumomediastinum: namely, the presence over the precordium of bubbling crepitations synchronous with the heart beat, the disappearance of cardiac dullness and appearance of subcutaneous emphysema. Since then other investigators<sup>4, 5, 6, 7</sup> have pointed out the diagnostic significance of the peculiar sounds and the mechanism of their production. It was, however, Hamman who first called attention of the medical profession to the clinical picture resulting from the spontaneous occurrence of mediastinal emphysema. As a result of his work there has been a considerable revival of interest in this subject. The literature now contains reports on the clinical features and pathologic physiology which have greatly increased our knowledge of its various aspects and contributed toward its recognition. This recognition in most cases is not difficult when the distinctive sounds heard over the heart and the roentgenographic evidence of air in the mediastinum are present.

Hamman,<sup>8</sup> in 1934, reported in detail three cases of mediastinal emphysema and gained the first widespread recognition for the condition to which his name is often applied. In 1937 he added four additional cases and omitted one of those previously reported in which the condition occurred following irrigation of a maxillary sinus.<sup>2</sup> The same year, Scott<sup>9</sup> reported two cases and called attention to the fact that the pain may simulate that of angina pectoris. In 1939 Hamman<sup>10</sup> added another to his series. Since

\* Received for publication January 31, 1944.

From the Medical Service, 333 Station Hospital, A.P.O. 827, United States Army.

then additional cases have been reported by McGuire and Bean,<sup>1</sup> Morey and Sosman,<sup>11</sup> Wolfe,<sup>12</sup> Matthews,<sup>13</sup> Pinckney,<sup>14</sup> Caldwell,<sup>15</sup> Styron,<sup>16</sup> Miller,<sup>17</sup> Murphy and Zeis,<sup>18</sup> Griffin,<sup>19</sup> Lintz,<sup>20</sup> Greene,<sup>7</sup> and Adcock.<sup>21</sup>

One of Scott's<sup>9</sup> cases in which the emphysema came on at the end of a hundred-mile cycle race, one reported by Greene,<sup>7</sup> and another by McGuire and Bean<sup>1</sup> in which the condition came on during childbirth, Wolferth and Wood's<sup>22</sup> patient in whom the symptoms came on during a wrestling match, and Lister's case<sup>23</sup> in which the chest roentgenograms, pleural effusion, and treatment suggested pulmonary tuberculosis should probably not be considered as true cases of spontaneous mediastinal emphysema.

In this paper we wish to add four more to the growing number of cases of spontaneous mediastinal emphysema which have been reported. The particular interest which attaches to our third and fourth cases is derived from the demonstration of an associated spontaneous pneumothorax.

#### CASE REPORTS

*Case 1.* A white male, aged 23, was admitted to the hospital on April 4, 1943, complaining of substernal discomfort. He dated the onset of his illness to April 2 when, while lying quietly in bed, he developed a sudden aching pain in the left chest, localized at the level of the third interspace in the midclavicular line. The pain was mild and did not prevent the patient from falling asleep. He attributed it at the time to indigestion, having eaten a hamburger two hours previously. He stated that he had not overexerted himself that day and did not feel tired although he had played two rounds (36 holes) of golf. He felt well the next day, although he again noticed the pain in the left chest that night while lying in bed. About 10 a.m. the next day while walking to the golf course, the pain reappeared with the same intensity, but extended toward the midsternum. At the third golf hole, the pain suddenly became worse and was described as a "heavy gas pain that wanted to be relieved." The pain was worse on deep inspiration, did not radiate toward the shoulders, arms or back and persisted until the patient arrived at the admitting ward.

Physical examination revealed a well-developed young adult who did not appear acutely ill. There was no evidence of dyspnea, orthopnea or cyanosis. Examination of the eyes, ears, nose and throat revealed no abnormalities. Ophthalmoscopic examination revealed normal discs, retina and vessels. The trachea was medial and thyroid gland not palpably enlarged. There was no evidence of subcutaneous emphysema of the neck or chest wall. The lungs were resonant to percussion, the breath sounds vesicular, voice sounds normal, and no râles were heard. The area of cardiac dullness was not enlarged, the outermost border extending 7 cm. to the left of the mid-sternal line in the fifth interspace. The sounds were distant, but of good quality. The second aortic sound was equal to the second pulmonic sound. No murmurs were heard. Over the entire precordium there were heard loud, crunching, crackling sounds more marked in systole, but also audible in diastole. These sounds were most evident over the sternum and left border of the heart and were not influenced by respiration or position. The patient stated that he could feel "noises in his chest" when the stethoscope was pressed against the precordial region. The heart rate was 80 per minute, and the rhythm was regular; arterial pressure 126 mm. Hg systolic and 78 mm. diastolic. The abdomen was soft and no organs nor masses were felt.

The next day, the patient still had some discomfort substernally but Hamman's sign was markedly diminished and best heard during full inspiration. A few

crepitations were still audible on the fifth hospital day and then disappeared. The patient's course was afebrile.

Laboratory Data. Urine: acid, clear, specific gravity 1.020, no albumin, sugar, cells or casts found. Blood: red blood cells 4,850,000 per cu. mm.; hemoglobin 90 per cent (Newcomer); white blood cells 7,250 with 80 per cent polymorphonuclears and 20 per cent lymphocytes. The blood sedimentation rate (Westergren) was 21 mm. after 45 minutes and 14 mm. on the third hospital day. Three stool specimens were negative for ova, parasites and occult blood. Electrocardiogram: sinus rhythm, rate 74 per minute, auriculoventricular conduction time 0.14 second. The QRS complexes 0.10 second, normal axis deviation. The T waves were high and upright in all leads and lead CF 4 was normal.

Roentgenograms revealed clear lung fields and a normal cardiovascular silhouette. There was no evidence of air in the mediastinum or in the soft tissues of the neck in the P-A or oblique views. There was no roentgenographic evidence of air in the retroperitoneal tissues.

Case 2. A white male, aged 21, was admitted to the hospital on May 8, 1943. He dated the onset of his illness to the previous evening when he drank half a pint of gin. Shortly thereafter he became nauseated and vomited several times. He continued to feel nauseated and vomited all that night and the next morning. He was unable to retain even water and about noon he developed numbness about the lips, hoarseness, sore throat and stiffness of the muscles of both hands. The vomiting gradually subsided and had ceased by the time the patient was admitted to the hospital at 4 p.m. At 8:30 p.m. while sitting quietly in bed, the patient took a drink of water and suddenly developed a sharp pain along the left costal margin and in the epigastrium which extended upward to the level of the second left rib. Within a few minutes it localized in the substernal region and he became conscious of palpitation, fluttering of the heart, and shortness of breath. The pain did not radiate but was worse on deep respiration and swallowing. He was also conscious of pain on both sides of the neck when he turned his head to either side. He felt hot, nervous, and perspired profusely. There was no history of any preceding respiratory infection or cardiovascular symptoms.

Physical examination revealed no abnormalities of the head, eyes, ears, nose or throat. Ophthalmoscopic examination revealed normal discs, retina and vessels. The thyroid gland was not enlarged and the trachea was medial. The soft tissues in both supraclavicular spaces were crepitant with infiltrated air. This was more marked on the left side where the subcutaneous crepitus extended from the anterior border of the left trapezius muscle to the angle of the jaw and down to the left clavicle. In the midline, crepitus was felt from the sternal notch to the level of the thyroid cartilage. On the right side, it was felt for a distance of 2 inches above the right clavicle. The lungs were resonant to percussion, the breath sounds vesicular, voice sounds normal and no râles were heard. There was no evidence of pneumothorax by physical examination. The point of maximum impulse of the heart could not be felt and the area of cardiac dullness was not determined, the dullness being replaced by a markedly hyperresonant percussion note. The sounds were distant. The rate was 88 per minute and rhythm was regular. No murmur was heard. Over the entire precordium and from the right mid-sternal line to the left anterior axillary line, peculiar, loud, crunching, crackling sounds were heard. They were systolic in time and were loudest during full inspiration. The arterial pressure was 132 mm. Hg systolic and 80 mm. diastolic. The abdomen was soft, and no organs or masses were felt. There was no costovertebral angle tenderness.

The next day, the patient still complained of discomfort under the sternum and pain along both sides of the neck especially on chewing movements of the jaw and on swallowing. The subcutaneous emphysema disappeared in 72 hours and Hamman's

sign in six days. The temperature on entry was 99.2° F., 98.8° for the first three days, then remained normal.

Laboratory Data. Urine: acid, clear, specific gravity 1.024, no albumin, sugar, cells or casts found. Blood: erythrocytes 5,050,000 per cu. mm.; hemoglobin 100 per cent (Newcomer); white blood cells 9,200 with 70 per cent polymorphonuclears, 26 per cent lymphocytes and 4 per cent eosinophiles. The blood sedimentation rate (Westergren) was 8 mm. after 45 minutes. Three stool specimens were negative for ova and parasites. Electrocardiogram: sinus rhythm, rate 83 per minute, auriculo-ventricular conduction time 0.14 second. The QRS complex 0.06 second, slight left axis shift. The T waves were high and upright in all leads and lead CF 4 was normal.

Roentgenograms revealed fairly extensive emphysema in the soft tissues on both sides of the neck, extending into the superior mediastinum (figure 1). In the P-A and oblique views, no pneumomediastinum could be demonstrated.

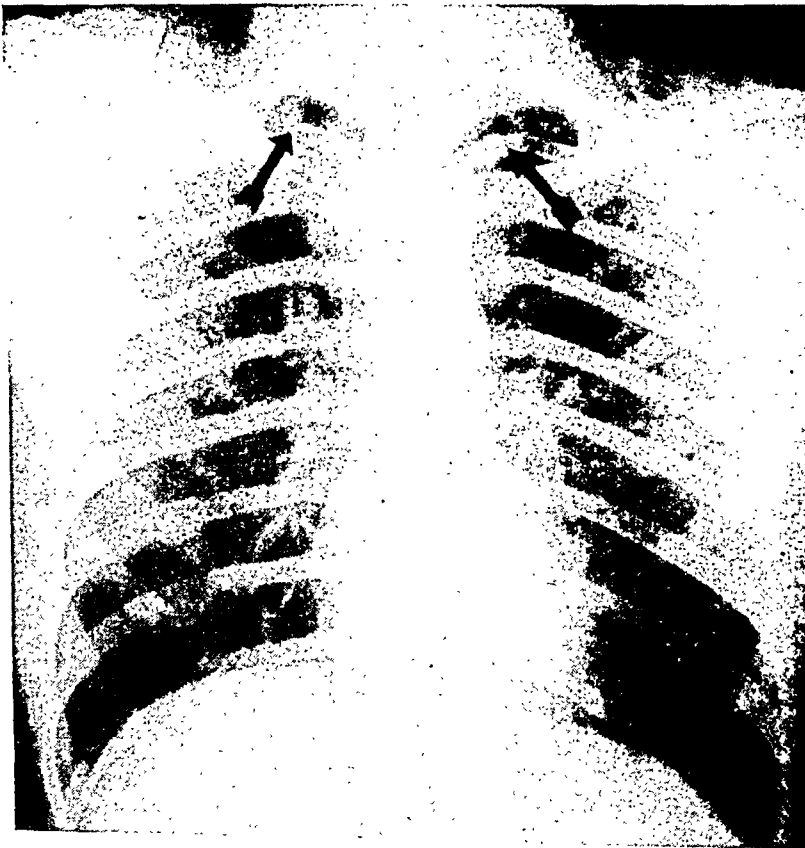


FIG. 1. Roentgenogram of the chest. The arrows indicate the air in the soft tissues of the neck extending from the superior mediastinum.

*Case 3.* A white Army officer, aged 28, was admitted to the hospital on October 14, 1940, complaining of pain in the left chest. On October 12 he suddenly developed a pain under the left scapula which rapidly spread to involve the left shoulder and entire left side of the chest. The pain was sharp, stabbing in character and was accentuated by movements of the body, deep inspiration and spasmodic spells of severe, hacking, non-productive cough. Associated with this pain he developed the sensation of a heavy weight within the chest and shortness of breath when he turned on his left side. He stated that since July he had suffered five moderately severe

upper respiratory infections. About July 20 and again in the latter part of August, he had developed pain in his right chest similar to that which he now had on the left side. Both of these subsided within a few hours. There were no symptoms referable to the gastrointestinal or genitourinary systems and nothing in his familial, past or systemic history to suggest a diagnosis of tuberculosis.

Physical examination revealed a well-developed adult who did not appear acutely ill. The pharynx was moderately injected. Chest expansion was slightly limited on the left side, the percussion note was hyperresonant and the breath sounds and voice sounds were diminished on the left side. No râles were heard. By percussion, the heart was normal in size and position. The heart sounds were distant, the rate 68 per minute, the rhythm regular, and no murmurs were heard. Over the lower left border of the sternum, there were audible "peculiar scratching, crackling sounds" in both systole and diastole, loudest in full inspiration. The arterial pressure was 120 mm. Hg systolic and 68 mm. diastolic. The abdomen was soft and no organs or masses were felt.

The patient's course in the hospital was afebrile. The pain disappeared within 24 hours and except for a slight cough, he was asymptomatic thereafter. Hamman's sign was audible on October 17 and 19 and then disappeared. He was discharged November 9, 1940.

Laboratory Data. Urine: amber, clear, acid, specific gravity varied between 1.012 and 1.020; no albumin, sugar, casts or cells were noted. Blood: erythrocytes, 4,180,000 per cu. mm. and hemoglobin 80 per cent. On entry, the white blood cells were 16,040 with 89 per cent polymorphonuclears, 1 per cent eosinophiles and 10 per cent lymphocytes. On October 16 it was 9,320 and on October 17, 5,920 with 72 per cent polymorphonuclears, 1 per cent basophiles and 27 per cent lymphocytes. The Wassermann and Kahn blood reactions were negative. Several smears were negative for malaria. The blood non-protein nitrogen was 35.1 mg. per cent and fasting blood sugar 96.0 mg. per cent. Thirteen examinations of the sputum were negative for tubercle bacilli.

On October 16\* radiographic examination revealed a partial pneumothorax on the left side. There was approximately 35 per cent collapse of the left lung. The heart and lungs were otherwise essentially normal. On October 24, roentgenographic examination revealed partial reexpansion of the left lung with approximately 20 per cent collapse remaining. A film on October 31 revealed complete reexpansion of the left lower lobe with slight compression of the left upper lobe by pneumothorax. There was no evidence of fluid and no parenchymal abnormalities noted. A film on October 31 revealed complete reexpansion of the left lung. Another film on November 20 was normal.

*Case 4.* A white soldier, aged 23, was admitted to the station hospital on December 13, 1943, complaining of pain in the left chest. He dated the onset of his present illness to 11 a.m. on the day of admission when, while walking down the road, he suddenly developed a sharp constricting type of pain over the left breast. The pain rapidly became worse over a period of 10 minutes and then rapidly subsided to be replaced by an aching pain just below the costal margin and in the supraclavicular region of the left chest. This pain was accentuated by any attempt to take a deep breath. A few minutes after the onset of the pain, he became short of breath. This was described as an inability to take a deep breath and lasted approximately 20 minutes. Both the pain and dyspnea were increased during the slight exertion of getting into the ambulance, but disappeared shortly after he resumed a recumbent position and did not recur. On December 10, the patient had developed a chest cold manifested by a slight, hacking, non-productive cough without any associated chest pain. He still had a slight cough at the time of entry. There was no history of familial tuberculosis, no personal history of hemoptysis, night sweats, fever or chill and he had gained approximately 10 pounds in weight during the past year.

Physical examination revealed a tall, fairly well-developed young male in no respiratory distress. The skin was clear and tanned. There were no abnormalities of the head, eyes, ears, nose or throat. The trachea was slightly deviated to the right side. Respiratory excursions of the left side of the chest were moderately diminished. Tactile fremitus was diminished over the entire left chest and percussion note was hyperresonant with extension of the hyperresonant note to the lowest position of the pleural space. The breath sounds and vocal fremitus were absent over the involved lung anteriorly and posteriorly. No râles were heard. The area of cardiac dullness was replaced by a hyperresonant percussion note and the right border could not be detected by percussion. The sounds were somewhat distant. The second pulmonic sound was louder than the second aortic sound. The rhythm was regular, the rate was 72 per minute and no murmurs or adventitious sounds were heard. The arterial pressure was 136 mm. Hg systolic and 80 mm. diastolic. The abdomen was soft and no organs nor masses were felt.

On December 19 the patient reported that he heard "peculiar sounds" in his left chest, and on December 21 the hospital radiologist, Captain Jerome L. Marks, reported the presence of air in the mediastinum. However, careful examination failed to reveal any change in the physical signs until the morning of December 22, when the typical crackling, crunching sounds were heard over the lower one-third of the sternum. These sounds were high pitched, present in systole and diastole, and were best heard with the patient in the upright position and in full expiration. The patient's course in the hospital was afebrile and asymptomatic. Hamman's sign persisted until January 6, but varied greatly in intensity and quality on different days.

Laboratory Data. Urine: acid, clear, specific gravity 1.012, no albumin, sugar and an occasional white blood cell per high power field. Blood: erythrocytes 5,150,000 per cu. mm.; hemoglobin 95 per cent (Newcomer); white blood cells 9,700 with 78 per cent polymorphonuclears and 22 per cent lymphocytes. The blood sedimentation rate (Westergren) was 5 mm. after 60 minutes.

An electrocardiogram on December 14, revealed a sinus mechanism with a rate of 64 per minute and an A-V conduction time of 0.18 second. The QRS complexes measured 0.08 second and the T waves were upright and normal in all leads.

Radiographic examination of the chest on December 13 revealed the presence of a left pneumothorax with approximately 50 per cent collapse of both lobes. There was a slight shift of the mediastinal structures to the right. On December 20 (figure 2) radiographic examination of the chest revealed approximately 35 per cent pneumothorax in the left thoracic cavity. There was still evident a slight shift of the mediastinal structures to the opposite side. There was also present a small collection of air between the pleura of the left lung and the cardiac silhouette in the region of the arc of the pulmonary artery and left auricle, indicative of mediastinal emphysema. On January 2 the left lung had completely reexpanded and there was no evidence of any parenchymal lesion.

*Pathologic Physiology.* The probable explanation of the genesis of spontaneous mediastinal emphysema is contained in the series of experiments of Macklin.<sup>24</sup> By artificially increasing the intrapulmonary pressure in a lobe of the lung of cats and other animals, he was able to demonstrate that the air enters the perivascular sheaths of the finer branches of the pulmonary vessels, presumably through the numerous minute ruptures in the walls of the alveoli. As the increased intrapulmonary pressure continues, the small bubbles of air coalesce into large ones as they move toward the root of the lung through the artificially produced channels in the vascular sheaths. At the root of the lung, the air bubbles may merge into large blebs which can



impede the pulmonary circulation. Further leakage causes these blebs to break through into the mediastinum. At times, the air in the perivascular sheaths may extend into the adjoining connective tissue and dissect a pathway toward the pleura where it forms a subpleural bleb, particularly in the region of the root of the lung. Rupture of this bleb may occasionally produce a pneumothorax.

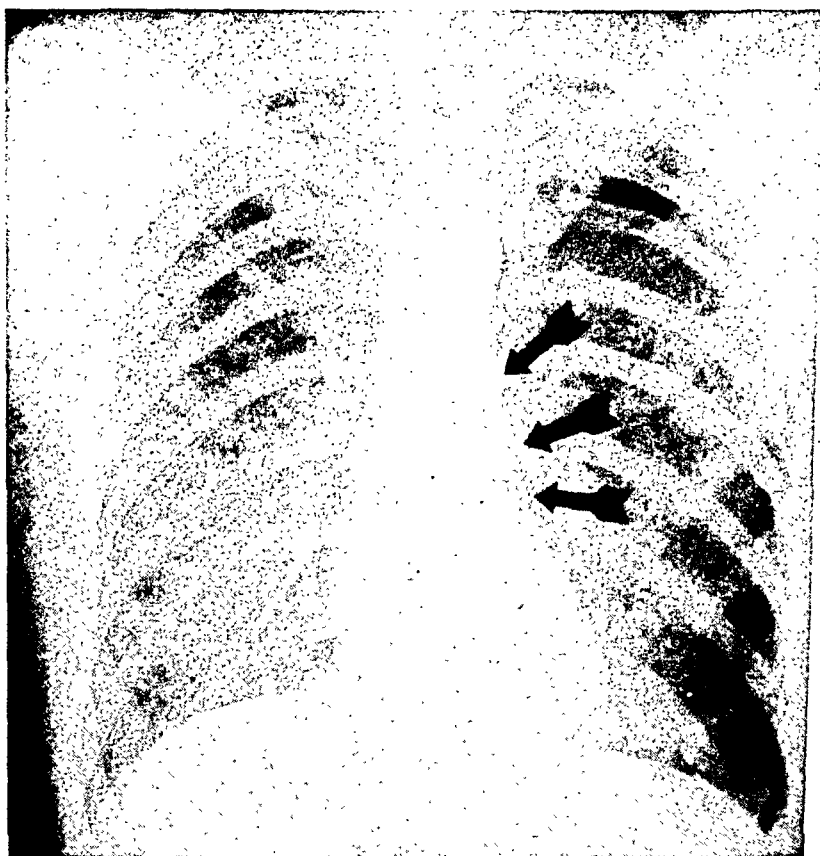


FIG. 2. Roentgenogram of the chest showing pneumothorax on the left side and an area of lessened density due to mediastinal emphysema.

The paths of extension of air in the mediastinum have been made the subject of special study by Ballou and Francis<sup>25</sup> and more recently by Macklin.<sup>24</sup> The air tends to follow with predilection the fascial planes, particularly the sheaths surrounding blood vessels. It may spread upward into the root of the neck, the face, axilla, anterior chest wall and arms. It is possible for it to dissect up along the sides of the trachea to the floor of the mouth extending under the base of the tongue which becomes elevated. It may extend forward between the parietal pleura and pericardium to appear as blebs overlying the heart, laterally into the opposite lung and downward into the retroperitoneal space where it may outline the kidneys, ureters and renal vessels.

*Diagnosis.* Clinically, the spontaneous type of mediastinal emphysema described by Hamman is characterized by the sudden development of pain in the chest in the absence of any antecedent trauma or unusual effort. The location and severity of the pain vary a great deal in different cases, depending largely on the degree of distention of the mediastinal tissues. It is usually described as severe, sharp, and stabbing although it may be mild, dull and aching in character. Occasionally there may be no associated pain.<sup>21</sup> Not infrequently pain in the left chest precedes the precordial pain. This has been attributed to interference with the blood flow in the pulmonary vessels of the lung by the pressure of air bubbles in the perivascular sheaths. The pain may radiate to the upper midback, shoulders, neck and occasionally down the left arm as it does in angina pectoris. There is also at times a pressure sensation under the sternum, and the patient may complain of pain on deep breathing, on swallowing, or on movement of the head. The duration of the pain is very variable, lasting from several hours to several days. Its character and radiation have at times led to the erroneous diagnosis of coronary occlusion. Macklin suggests that this radiation is due to pressure on the coronary vessels through both layers of the pericardium whereas Scott believes it is due to pressure of the mediastinal air on the aorta and surrounding tissues.

The patients frequently prefer certain positions in which the pain is decreased. Dyspnea, cyanosis, and orthopnea may occur but are not characteristic of the spontaneous cases of mediastinal emphysema. In uncomplicated cases there is no clinical evidence of serious constitutional disturbance. Occasionally the temperature may be elevated for the first few days, but the blood pressure, white blood counts, sedimentation rate and electrocardiogram are usually within normal limits.

The demonstration of air in the subcutaneous tissues of the neck and anterior chest wall by palpation is diagnostic. The area of cardiac dullness is often diminished or completely obliterated, being replaced by a hyperresonant percussion note.

The pathognomonic sign of mediastinal emphysema is the peculiar sound heard over the pericardium on stethoscopy and sometimes even with the unaided ear. It has been variously described as crunching, crackling, popping, clicking, tapping, snapping, crepitant, etc., and is synchronous with the heart beat. This has been termed Hamman's sign and attributed by him to the action of the heart on air between the anterior parietal pericardium and the chest wall. Macklin's experimental studies corroborated this clinical impression. When he removed the sternum in his experimental animals, a froth of bubbles was found over the parietal pericardium. The sound has been likened to the "squeak of a leather saddle," "rubbing two inflated balloons together," "crackling of cellophane," etc. Changes in position and phase of respiration may cause a change in the intensity of the noises. It is usually heard during systole but may also be heard during diastole.

Pneumothorax was present in some of the reported cases of mediastinal emphysema. It is usually small and not detected except by roentgenograms of the chest. Pneumoretroperitoneum is very common in experimental animals and has been reported following traumatic emphysema in man. In Adcock's case,<sup>21</sup> the retroperitoneal emphysema was quite extensive, and the air could be felt in the pararectal tissues by digital examination. The condition was also suspected in one of Griffin's cases in whom upper abdominal pain, an area of tympany in the left upper abdomen and tenderness over this area were present.

Roentgenographic demonstration of air in the mediastinum is diagnostic. In the anteroposterior view only the outlying pockets of air may be seen, so that lateral and oblique views should also be taken. In the anteroposterior view, a sharp line running parallel to the outer wall of the mediastinum in the presence of a pneumothorax may be detected. In the lateral and oblique views, air may be visible between the heart and the anterior chest wall or in the posterior mediastinum. In rare cases when the air does not extend forward around the heart, Hamman's sign may be absent and the roentgenographic evidence of air in the mediastinum may be decisive. Air may also be detected in the subcutaneous tissues of the neck and in the retroperitoneum.

In the differential diagnosis, coronary occlusion, pericarditis, dissecting aneurysm and pulmonary embolus must be considered. These can usually be differentiated by physical examination, roentgenographic examination of the chest and electrocardiography.

Treatment is symptomatic and the prognosis, in general, is excellent. Resorption of air from the mediastinum is rapid when the point of entry is closed. It is possible that in the future some of the complications occurring in experimental animals may develop in man. If a large amount of air should escape from the lung, the pressure in the mediastinum could produce circulatory embarrassment and necessitate active treatment such as the induction of an artificial pneumothorax or incision to allow the air to escape externally. Infection from the alveoli along false channels may produce pneumonia and even mediastinitis.

## DISCUSSION

There is increasing evidence that the syndrome under discussion occurs more frequently than the number of reported cases indicate. The cases presented conform closely to the previously established criteria for diagnosis. The most constant feature is the peculiar and distinctive sound heard over the heart synchronous with its contractions. In the majority of reported cases, no definite evidence of pulmonary disease has been demonstrated. Macklin has suggested that small areas of atelectasis, by causing over-distention of the surrounding alveoli, may lead to escape of air into the perivascular sheaths. No such areas of atelectasis could be demonstrated in the roent-

genograms of any of the four cases. However, the author has recently seen a case in which this was undoubtedly the mechanism of production of mediastinal emphysema. This patient was seen after he had recovered from his acute illness.

*Case 5.* A white male, aged 21, was admitted on March 22, 1943, with the diagnosis of chronic, bilateral, follicular tonsillitis. On March 23, 1943, a bilateral tonsillectomy was performed under 1 per cent novocaine anesthesia. At 1:30 a.m. on March 24, the patient was seen by a physician because of severe precordial pain, cyanosis, and cough productive of frothy, brownish-red sputum. On examination, the patient was dyspneic, cyanotic and in marked distress. The trachea was deviated to the right side, dullness to percussion and absent breath sounds were elicited over

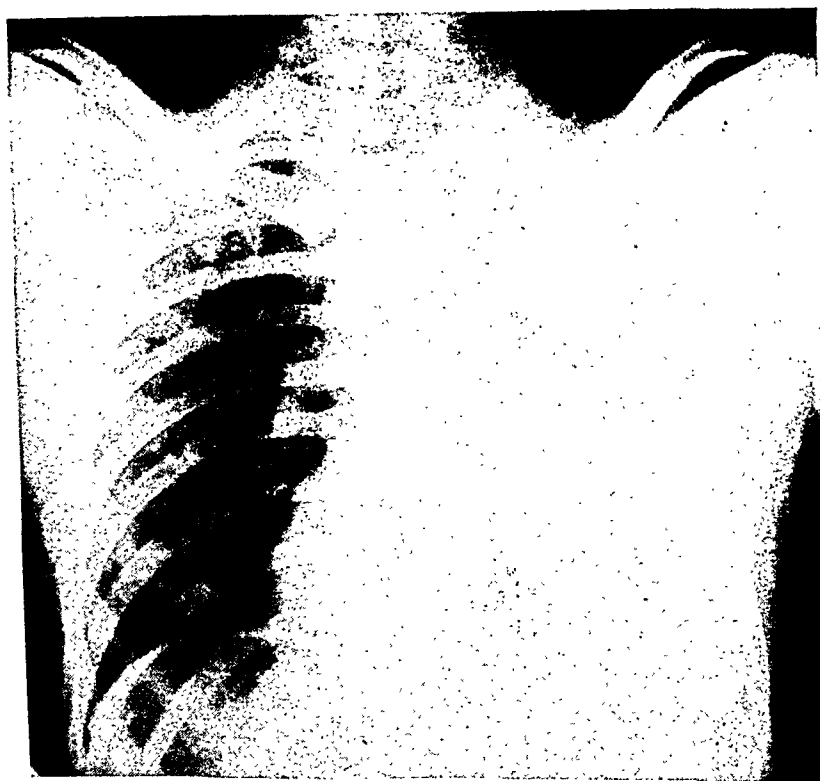


FIG. 3A. Roentgenogram of the chest taken March 24 revealing massive atelectasis of the right lung with shift of the mediastinal contents to the affected side.

the right middle and lower lobe. The area of cardiac dullness was displaced to the right and the basal heart sounds were best heard below the right clavicle. Over the third rib and interspace parasternally there was audible a peculiar sound described by various observers as a "clicking sound suggestive of a pericardial rub," "a high-pitched pleuro-pericardial friction rub," and a "pericardial friction rub." The temperature rose to 102° F. The leukocyte count was 25,600 with 85 per cent polymorphonuclears and 15 per cent lymphocytes. A roentgenogram of the chest taken March 24 (figure 3A) revealed marked retraction of the trachea, mediastinum and heart toward the right side. The entire right lung was atelectatic and the right diaphragmatic shadow obliterated. The diagnosis was "massive atelectasis of the right lung." An electrocardiogram revealed right axis shift, and flattening of the T waves in all leads.

On March 24, under 5 per cent novocaine spray anesthesia, a rubber catheter was inserted in the trachea and a large amount of mucopurulent material was aspirated by suction with marked clinical improvement. The next day, the procedure was repeated and some more mucopurulent material was aspirated from the right main bronchus. On March 25, the roentgenogram of the chest (figure 3B) revealed that the heart and mediastinum had returned to their normal position and the right lung was almost completely aerated. Incidentally, the presence of subcutaneous emphysema on both sides of the neck was reported. At this time, the air in the subcutaneous tissues of the neck was detected clinically and a note was made that the patient complained of severe pain in the neck. The subcutaneous emphysema slowly disappeared



FIG. 3B. Roentgenogram on March 25 shows reexpansion of the right lung with the presence of subcutaneous emphysema on both sides of the neck.

and the patient improved rapidly. Roentgenograms of the chest on March 29 and April 4 were normal, and an electrocardiogram on April 1 was also within normal limits.

The findings in this case can be explained by overdistention of the left lung following postoperative massive atelectasis of the right lung. The alveolar ectasia in the left lung permitted the air to escape into the perivascular sheaths and lead to mediastinal and subcutaneous emphysema. The careful pathologic study by Fisher and Macklin<sup>26</sup> of a child with foreign body atelectasis of the lung supports this theory of the mechanism of formation of mediastinal emphysema.

Although it is now generally appreciated that spontaneous pneumothorax

may occur in the absence of any preëxisting pulmonary disease, the etiology of the condition is still obscure. One of the most commonly accepted theories is that of rupture of emphysematous blebs occurring on the surface of the pleura. In his experimental animals, Macklin noted the penetration of air from the perivascular sheaths into the connective tissue and eventually to the pleura where it formed a subpleural bleb. More commonly however, pneumothorax was due to the escape of air from the mediastinum. He was able to demonstrate that the air reaches the pleural cavity via a tear in the mediastinal wall. He was able to force air from the mediastinum into the pleural cavity, but by increasing the intrapleural pressure after induction of a pneumothorax, he was never able to get air to penetrate the mediastinum.

Hamman suggests that his mechanism—rupture of air from the mediastinum into the pleural cavity—is a better explanation for the development of some cases of benign spontaneous pneumothorax than the theory of a ruptured subpleural bleb. Physiologically, the pneumothorax may be beneficial. By collapsing the lung, it stops further leakage of air into the vascular sheaths, relieves the pressure on the mediastinal structures and frees the circulation in the lungs.

It is of interest that the pneumothoraces present in cases 3 and 4 were large enough to be detected on physical examination. Usually they are detected only by radiographic examination of the chest. As in previously described cases, the pneumothoraces were on the left side. Hamman predicts that in the future, they will probably be found on the right side as well.

In each case the diagnosis was made by detection of the typical sounds over the heart. As has been pointed out previously, these sounds may show great variation in intensity and quality during the course of the condition. They may be detected some time after the appearance of spontaneous pneumothorax and may last for several weeks.

#### SUMMARY

The literature regarding the clinical picture and pathologic physiology of spontaneous mediastinal emphysema has been reviewed. Four additional cases illustrating the essential clinical picture of the syndrome are reported. In two of these, an associated spontaneous pneumothorax was demonstrated. Another case report of mediastinal and subcutaneous emphysema following atelectasis of the lung lends further support to Macklin's theory as to the underlying mechanism of spontaneous mediastinal emphysema.

#### BIBLIOGRAPHY

1. MCGUIRE, J., and BEAN, W. B.: Spontaneous interstitial emphysema of the lungs, *Am. Jr. Med. Sci.*, 1939, cxcvii, 502-509.
2. HAMMAN, L.: Spontaneous interstitial emphysema of the lungs, *Trans. Assoc. Am. Phys.*, 1937, lii, 311-319.
3. MÜLLER, F.: Ueber Emphysem des Mediastinum, *Berl. klin. Wchnschr.*, 1888, xxv, 205-208.

4. REES, W. A., and HUGHES, G. S.: Wounds of the chest as seen at an advanced operating center, *Lancet*, 1918, i, 55-59.
5. SMITH, S. M. S.: Pericardial knock, *Brit. Med. Jr.*, 1918, i, 78.
6. MUNDEN, W. P. H.: Pericardial knock, *Brit. Med. Jr.*, 1918, i, 174.
7. GREENE, J. A.: Unusual sounds emanating from the chest, *Arch. Int. Med.*, 1943, lxxi, 410-414.
8. HAMMAN, L.: Remarks on the diagnosis of coronary occlusion, *Ann. Int. Med.*, 1934, viii, 417-431.
9. SCOTT, A. M.: The significance of the anginal syndrome in acute spontaneous pneumomediastinum, *Lancet*, 1937, i, 1327-1330.
10. HAMMAN, L.: Spontaneous mediastinal emphysema, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 1-21.
11. MOREY, J. B., and SOSMAN, J. C.: Spontaneous mediastinal emphysema, *Radiology*, 1939, xxxii, 19-22.
12. WOLFE, B. P.: Spontaneous interstitial emphysema of the lungs, *Ann. Int. Med.*, 1940, xiii, 1250-1252.
13. MATTHEWS, E. P.: Spontaneous mediastinal emphysema, *New Orleans Med. and Surg. Jr.*, 1941, xciii, 523-524.
14. PINCKNEY, M. M.: Mediastinal emphysema and idiopathic spontaneous pneumothorax, *Virginia Med. Monthly*, 1941, lxviii, 315-319.
15. CALDWELL, H. W.: Spontaneous mediastinal emphysema, *Jr. Am. Med. Assoc.*, 1941, cxvi, 301-302.
16. STYRON, C. W.: Spontaneous mediastinal emphysema, *New England Jr. Med.*, 1941, ccxxv, 908-909.
17. MILLER, U.: Spontaneous interstitial emphysema of the lungs, *Ohio State Med. Jr.*, 1941, xxxvii, 1056-1059.
18. MURPHY, J. P., and ZEIS, L. B.: Spontaneous interstitial mediastinal emphysema, *Jr. Missouri Med. Assoc.*, 1942, xxxix, 5-7.
19. GRIFFIN, R. J.: Spontaneous pneumothorax, *Kentucky Med. Jr.*, 1941, xxxix, 284-288. A diagnostic sign of interstitial emphysema of the mediastinum, *Ann. Int. Med.*, 1942, xvii, 295-297.
20. LINTZ, R. M.: Spontaneous mediastinal emphysema, *Arch. Int. Med.*, 1943, lxxi, 256-261.
21. ADCOCK, J. D.: Spontaneous interstitial emphysema of the lung with mediastinal, retroperitoneal and subcutaneous emphysema, *Arch. Int. Med.*, 1943, lxxi, 650-657.
22. WOLFERTH, C. C., and WOOD, F. C.: Angina pectoris, *Med. Clin. North Am.*, 1930, xiii, 947-967.
23. LISTER, W. A.: A case of pericardial knock associated with spontaneous pneumothorax, *Lancet*, 1928, i, 1225-1226.
24. MACKLIN, C. C.: Pneumothorax with massive collapse from experimental local over-inflation of the lung substance, *Canad. Med. Assoc. Jr.*, 1937, xxxvi, 414-420. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: clinical implication, *Arch. Int. Med.*, 1939, lxiv, 913-926. Impediment to circulation occasioned by pulmonic interstitial emphysema and pneumomediastinum, *Jr. Mich. Med. Soc.*, 1940, xxxix, 756-759.
25. BALLON, H. C., and FRANCIS, B. C.: Consequences of variations in mediastinal pressure: mediastinal and subcutaneous emphysema, *Arch. Surg.*, 1929, xix, 1627-1659.
26. FISHER, J. H., and MACKLIN, C. C.: Pulmonic interstitial and mediastinal emphysema: report of a fatal case in which the emphysema occurred in a child as a result of the aspiration of peanut fragments, *Am. Jr. Dis. Child.*, 1940, lx, 102-115.

# SPONTANEOUS PNEUMOTHORAX: A REPORT OF THREE UNUSUAL CASES \*

By ALFRED GOLDMAN, M.D., F.A.C.P., and HAROLD ROTH, M.D.,  
*St. Louis, Missouri*

RECENTLY there were encountered on the Ward Service of the Barnes Hospital three patients with spontaneous pneumothorax, each of whom exhibited complications which seemed of sufficient interest to us to warrant reporting. The first patient was a 51 year old man with congenital cystic disease of the lung. Treatment in this case proved to be of particular interest. The second patient suffered a spontaneous pneumothorax with complete atelectasis of the left upper lobe. This complication has been reported only once before. The third patient had a spontaneous hemopneumothorax with recovery followed two months later by a spontaneous pneumothorax. It has generally been assumed that the occurrence of spontaneous pneumothorax after hemopneumothorax is impossible because of the formation of adhesions. Although the cases present unrelated aspects of spontaneous pneumothorax, it was decided to group them together for the sake of brevity.

## CASE REPORTS

*Case 1.* M. B., a 51 year old Polish barber, entered Barnes Hospital August 1, 1942. His past history was significant in that between the ages of 26 and 28 he worked in a copper mine tunnelling through quartz. At this time he began to cough up sputum flecked with black particles. At the age of 32 he stated that he was found to have syphilis for which he received apparently adequate treatment. The patient then felt well until the age of 41, when he developed attacks of shortness of breath. These would last up to two hours and come as often as every two weeks to two months. At the age of 45, he had an attack of dyspnea lasting three weeks and associated with severe pain in the right side of the chest.

The patient's present attack of dyspnea began two weeks prior to his admission and was the most severe attack that he had experienced. He stated that he had a moderate cough, productive of a tablespoonful of gray, black flecked sputum a day, and a dull pain in the right chest, for the past six months.

*Physical Examination.* Temperature 38.4° C. Pulse 100. Respirations 28. Blood pressure 124 mm. Hg systolic and 94 mm. diastolic. The patient was markedly orthopneic, dyspneic, and moderately cyanotic. The important physical findings were limited to the chest. The trachea was deviated to the left. There was slight lag of the right side of the chest. Percussion note over the right was tympanitic while the breath sounds, voice sounds, and tactile fremitus were markedly diminished. The left lung was essentially negative. The heart was displaced to the left.

*Laboratory Findings.* Blood count: red blood cells 5,300,000, hemoglobin 13.4 grams; white blood cells 9,250, differential count normal. Urine negative. Kahn reaction negative. Five sputa negative for tubercle bacilli. Vital capacity 1,600 c.c.

\* Received for publication April 16, 1943.

From the Department of Internal Medicine, Washington University School of Medicine and the Barnes Hospital, St. Louis, Missouri.



Roentgenographic examination of the chest, August 8, 1942, showed a large pneumothorax pocket in the right chest with almost complete collapse of the lower portion of the right lung (figure 1). The apical portion of the right lung was held up by adhesions. The upper portion of the right lung field revealed numerous areas of decreased density having very thin walls about them. Several of these areas were also noted in the upper portion of the left lung field. Lipiodol bronchograms did not show any filling of the cystic areas.

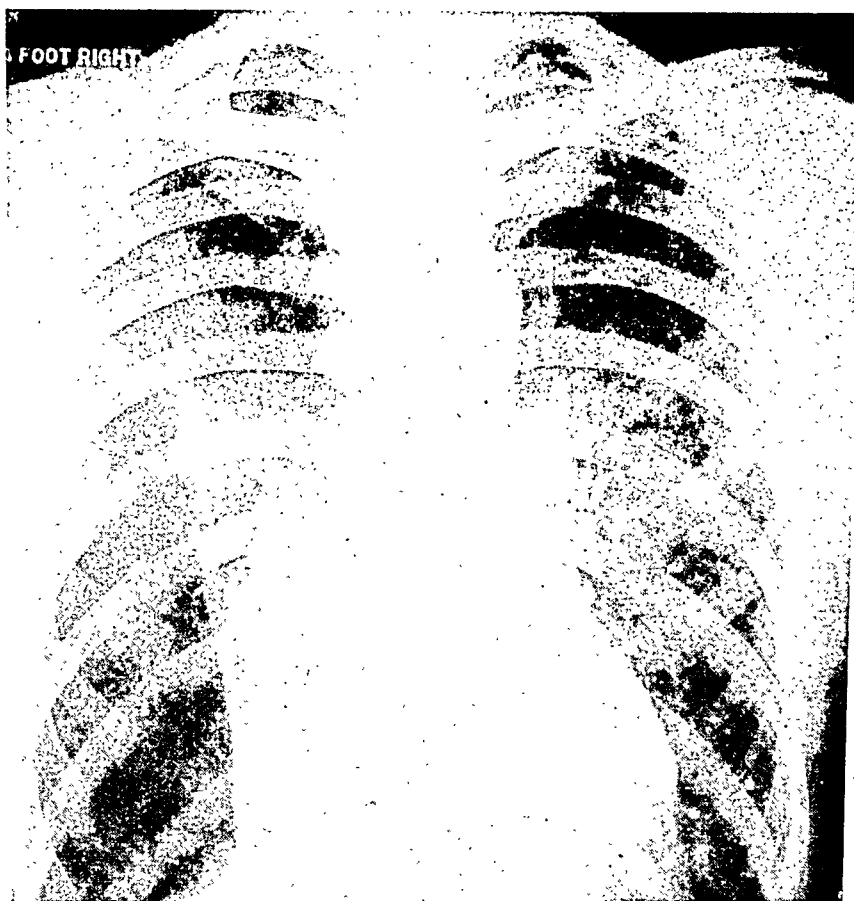


FIG. 1. (Case 1, 8/3/42) Spontaneous pneumothorax associated with cystic disease of the lung. Note rarefied areas in both apices.

*Course in the Hospital.* The patient's temperature dropped to normal on his first hospital day. Because of the severe dyspnea, 250 c.c. of air were removed from the right chest on August 4, 1942. The initial pressure reading was minus 5 plus 5; the final pressure reading was minus 10 plus 3. There was no immediate relief. From August 4 to August 18, there was no evidence of reexpansion. On August 18, 1,000 c.c. of air were aspirated with a final pressure reading of minus 15, minus 5, and at the same time 15 c.c. of the patient's whole blood were injected into the right pleural space. On August 11, the patient's vital capacity was 3,100 c.c. and his pneumothorax was no longer evident.

He was discharged on August 22, 1942, completely relieved of his chest pain and dyspnea (figure 2).

*Comment.* It is difficult to distinguish between congenital cystic and acquired cystic disease of the lung. In this case dyspnea was first noted at the age of 41, the patient apparently being free of all symptoms up to that time. Although this would suggest an acquired origin, it has been pointed out many times that patients with congenital cystic disease of the lung may have no symptoms until late in life. In a recent review<sup>1</sup> of 374 cases of cystic disease of the lung, it was stated that 207 of the cases were first noted

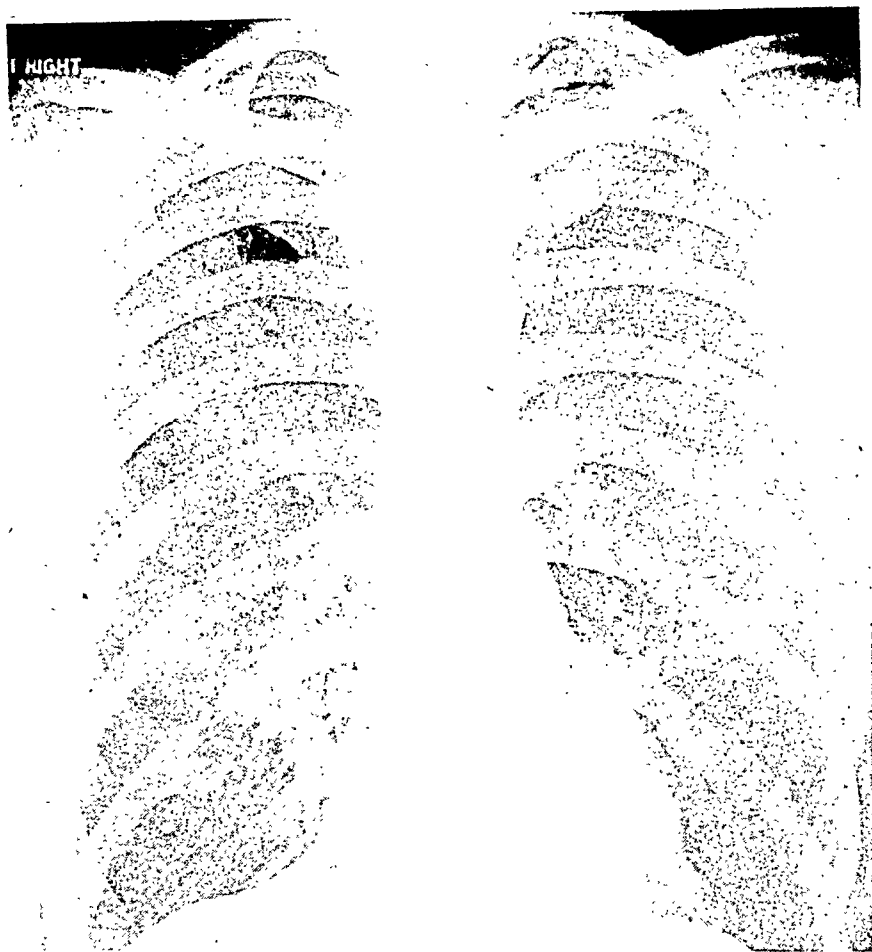


FIG. 2. (Case 1, 12/29/42) Complete reëxpansion of the right lung with cystic areas evident in both upper lobes.

after 15 years of age. The roentgenographic film of the lungs showed evidence of cystic change within both lungs as well as peripheral cysts. This would indicate that the cystic change was not wholly, at least, due to emphysematous bullae. There was no history of asthma as a cause for emphysematous bullae. The lipiodol studies showed no evidence of bronchiectasis. There was no evidence in the history that pneumonitis played any part in the causation of the cysts. The roentgenogram showed a mild degree of silicosis which, however, did not seem to have produced sufficient fibrotic changes in

the lung to cause the cysts. Therefore, it seems most likely that we are dealing with a case of congenital cystic disease of the lung.

The frequent short attacks of dyspnea which the patient experienced were probably due to an increase in air pressure within one or more cysts, so called "tension cysts." The episode of dyspnea and chest pain lasting for three weeks, which occurred at the age of 45, may have been due to a spontaneous pneumothorax which resolved.

Schenck,<sup>2</sup> in his recent review of congenital cystic disease of the lung, states that the occurrence of spontaneous pneumothorax in congenital cystic disease is rare in the adult, more common in children.

The history of exposure to silica and the moderate radiographic changes in the lung fields suggested the diagnosis of silicosis. Spontaneous pneumothorax is known to occur occasionally in this condition, 3.5 per cent in one series.<sup>3</sup> The slight degree of silicosis in this case, however, probably eliminates this as a cause for the spontaneous pneumothorax.

The treatment of this case was similar to the handling of all cases of tension pneumothorax: early aspiration of air because of the patient's severe dyspnea. This, however, did not relieve the patient, and it was assumed, therefore, that the perforation had not had sufficient time to heal. He was placed at rest and watched closely. Two weeks later the removal of 1,000 c.c. of air quickly deflated the pneumothorax and the injection of the patient's blood was done to produce pleural adhesions and prevent, if possible, a recurrence of the pneumothorax. Blood has been successfully used by Watson and Robertson<sup>4</sup> to produce pleural adhesions. Other substances<sup>5</sup> which may be used are 30 to 67 per cent glucose, iodized oil, 1/2 per cent solution of silver nitrate, oil of turpentine, guaiacol in iodoform, iodized talc, and plain talc.<sup>6</sup>

*Case 2.* T. A., a 40 year old mechanic, was admitted to Barnes Hospital April 9, 1942. From 1918 to 1924, he had been a coal miner. In 1924 he had had a sudden attack of intense pain in the right side of the chest. The symptoms were severe for several days, then gradually disappeared during the next four months. The patient then remained in good health until June 1941, when he had a sudden attack of severe pain in the anterior part of the left side of his chest, accompanied by a cough and marked dyspnea. He attributed this attack to a severe paroxysm of coughing. The pain gradually disappeared, but the dyspnea persisted up to the time of admission to the hospital.

*Physical Examination.* Temperature 37.4° C. Pulse 90. Respirations 24. Blood pressure 125 mm. Hg systolic and 80 mm. diastolic. The significant findings were in the chest. There was a marked lag of the left side of the chest, percussion note was hyperresonant throughout the left side, breath sounds and tactile fremitus were absent. The trachea was deviated to the right. The heart was markedly displaced to the right.

*Laboratory Findings.* Blood count was normal, Kahn reaction negative, and urinalysis negative.

Roentgenographic examination of the chest (figure 3) showed a left-sided pneumothorax with an apparently completely collapsed left upper lobe, and a moderately collapsed left lower lobe which extended to within 3 cm. of the lateral

chest wall. The suspected left upper lobe could be seen as a small dense tumor-like mass in the left hilus region. The heart and mediastinal structures were markedly displaced to the right. Bronchogram of the left chest showed that the left upper lobe bronchus entered the mass noted on the roentgenogram, proving that it was the left upper lobe (figure 4).

*Course in Hospital.* Because of the dyspnea, 250 c.c. of air were removed from the left side of the chest. Initial pressure was minus 5 centimeters of water, zero; final pressure reading was the same. No expansion of the lung could be demonstrated following the removal of air, nor was there any relief of the patient's dyspnea.

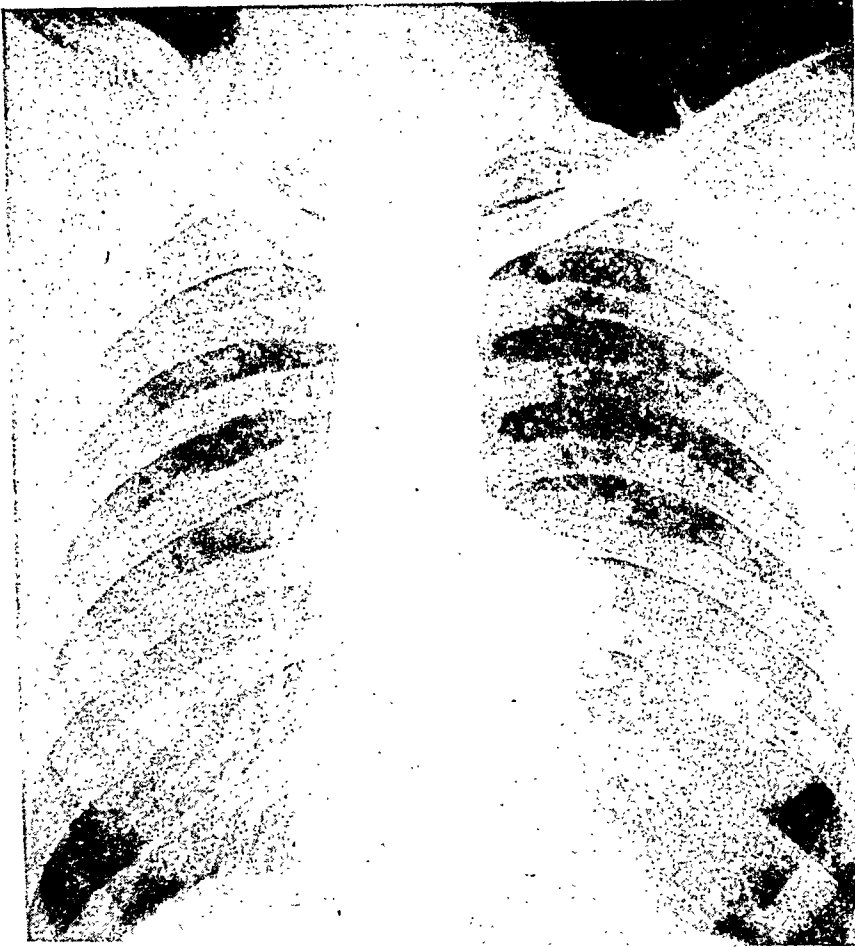


FIG. 3. (Case 2, 4/11/42) Spontaneous pneumothorax with complete collapse of the left upper lobe and partial collapse of the left lower lobe.

Because of the atelectasis, a bronchoscopy was performed on April 20, 1942, at which time the mucosa of the carina was noted to be thickened. A small amount of mucoid secretion was present in the left upper main bronchus. This was aspirated but showed no significant findings. A biopsy of the thickened mucosa showed only small round cell infiltration, no tumor cells.

On April 21, 1942, 400 c.c. of air were removed from the left side of the chest. The initial pressure was plus 2, minus 10 centimeters of water, final pressure, minus 4, minus 7. The patient was discharged on April 22, 1942, without any apparent subjective or objective improvement.

On June 15, 1942, the patient returned to the chest clinic completely relieved of his symptoms. Roentgenographic examination of his chest showed complete expansion of his entire left lung (figure 5). The lung fields were perfectly clear throughout. The patient remained well up to his last observation on January 5, 1943.



FIG. 4. (Case 2, 4/14/42) Lipiodol bronchogram showing mass to be left upper lobe.

*Comment.* This is a case of idiopathic spontaneous pneumothorax. The history would indicate that the present attack is of 10 months' duration. Although it is well known that the average case of idiopathic spontaneous pneumothorax clears up within four to eight weeks, a small percentage may remain chronic,<sup>7</sup> even lasting for years, and we feel that this case is of the latter, or chronic type.

The most interesting feature of the case is the complete collapse of the left upper lobe with the relatively mild collapse of the left lower. A similar but less striking picture may be seen in the selective collapse occurring at times during pneumothorax therapy for pulmonary tuberculosis.

J. Palocio and E. S. Mazzei,<sup>8</sup> in 1941, stated that they were the first to report cases of atelectasis occurring during the course of spontaneous pneumothorax. They report four cases. Two of the cases were similar to ours in that one involved only the upper lobe, and the other involved only the lower lobe; the other two were said to show atelectasis of the entire lung. There was a definite difference between these cases and ours in that there was complete recovery in all four cases within 20 days. The author believed that the atelectasis was due to vagal stimulation by the spontaneous pneumothorax.

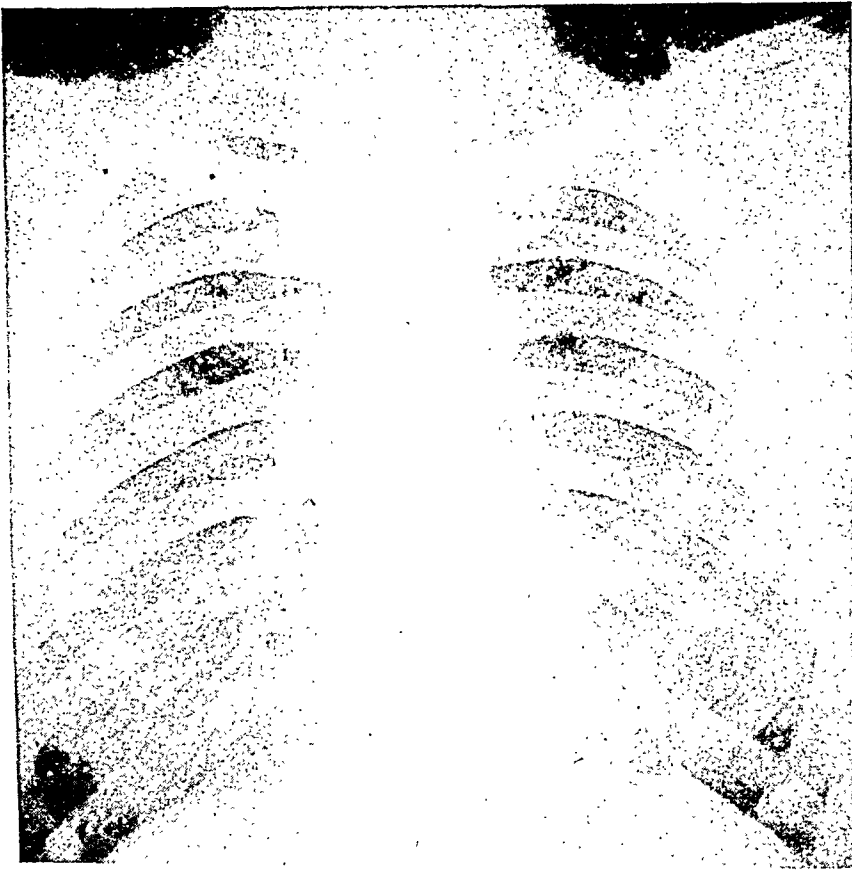


FIG. 5. (Case 2, 6/15/43) Complete reëxpansion of the left lung.

Escudero and Adams<sup>9</sup> have shown that atelectasis produced experimentally in dogs may be followed by spontaneous pneumothorax, probably due to air passing through the anatomically thin mediastinum; but they themselves indicate that this is probably not applicable to human beings.

There are several case reports of postoperative atelectasis, and atelectasis occurring during the course of pneumonia, followed by spontaneous pneumothorax. In all these cases the authors felt that the collapse occurred first and the pneumothorax later. The history in our case would indicate that we are

dealing with a case of primary pneumothorax, as there was no cause for sudden atelectasis.

The complete collapse of the left upper lobe and the subsequent re-expansion following bronchoscopy would suggest that we were dealing with a bronchial obstruction which was relieved by the bronchoscopic procedure. Inasmuch as there was only a moderate amount of mucus removed from the bronchus, we felt that there may have been an additional element in the form of kinking of a bronchus.

*Case 3.* C. H., a 28 year old engineer, entered Barnes Hospital on May 20, 1942. His past history was noncontributory. On May 19, 1942, while shoveling dirt, he noticed a sudden sharp pain in the upper anterior part of the right side of his chest radiating to his upper abdomen. The pain diminished for a short time but recurred the following day with gradually increasing dyspnea, and he was, therefore, sent to the hospital.

*Physical Examination.* Temperature 38.2° C. Pulse 95. Respirations 26. Blood pressure 130 mm. Hg systolic and 70 mm. diastolic. The patient appeared ill, was dyspneic and slightly cyanotic. The chief physical findings were confined to the chest. There was a marked lag of the right side of the chest which was tympanitic down to the level of the eighth rib posteriorly, below which the percussion note was flat. The breath sounds and voice sounds were absent over the entire right side. The heart and mediastinal structures were markedly displaced to the left.

*Laboratory Findings.* Blood count: red blood cells 3,900,000, hemoglobin 78 per cent, white blood cells 12,300; differential count: "stab" forms 18, segmented neutrophils 56, lymphocytes 23, monocytes 3. Kahn reaction negative.

Roentgenographic examination of the chest on May 21, 1942, showed a hydro-pneumothorax on the right with a fluid level at the anterior end of the fourth rib. There was a marked collapse of the right lung with a pleural adhesion at the apex (figure 6).

*Course in Hospital.* On May 20 the right pleural cavity was aspirated and hemorrhagic fluid was obtained. The red blood cell count on the fluid was 5,000,000. The white blood cell count was 8,800. Culture of the fluid was sterile and guinea pig inoculation was negative.

From May 20 to June 1, 1,800 c.c. of fluid were removed from the chest, and at the same time 450 c.c. of air were replaced. By June 6, almost complete re-expansion of the lung had taken place. The patient's temperature was 38° C. for the first five days, then gradually returned to normal. He was discharged from the hospital to the Outpatient Department on June 8.

Fluoroscopic observation on June 13, 1942, showed that the lung had completely expanded, although there was a small amount of fluid at the right base. On July 11, 1942, there was no longer any fluid. On August 8, the patient returned to the clinic when he reported that on July 23, while lifting a studio couch, he suddenly developed a sharp pain in his right chest associated with dyspnea. This lasted 30 minutes. He called his local doctor who took roentgenograms of his chest and found that he had a pneumothorax. Our examination on August 8 showed that he had a right sided pneumothorax with about 50 per cent collapse of the right lung and a small amount of fluid in the right costophrenic angle. He was relatively comfortable at this time. On September 20, 1942, he had a 20 per cent collapse without fluid. On October 17, the lung had completely re-expanded. Careful study of the lungs following re-expansion showed no clinical or roentgenological evidence of tuberculosis.

*Comment.* This is a case of spontaneous idiopathic hemopneumothorax, a relatively rare condition. Hartzell<sup>11</sup> states that there were 40 reported undisputed cases of spontaneous hemopneumothorax up to 1942, which with his three cases made 43. There are unquestionably many other unreported cases of which we have seen several. The condition occurs characteristically, as in this case, in the young, healthy adult male.

The accepted opinion of the origin of a spontaneous hemopneumothorax is that it is due to the rupture of a valve vesicle situated near the pleural

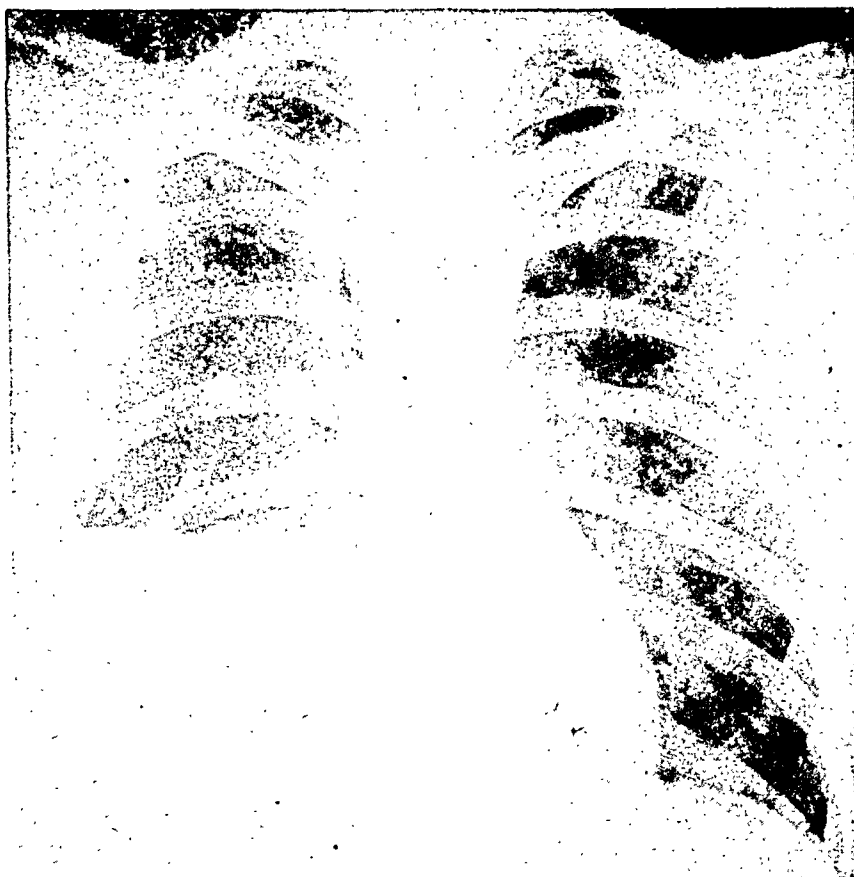


FIG. 6. (Case 3, 5/21/42) Spontaneous hemopneumothorax.

surface, followed by a short period of improvement, then recurrence of pain, dyspnea, and shock-like symptoms, depending, of course, on the amount of blood lost.

The treatment of a case of spontaneous hemopneumothorax must be individualized. When there is a considerable amount of fluid present it is usually wise to remove fluid in order to relieve pressure on the mediastinum. At the same time care must be taken not to reduce the intrapleural pressure too greatly because of the danger of opening up an incompletely healed fistula, and thus causing an increase in the bleeding and of the pneumothorax.



This can be prevented by the introduction of a relatively small amount of air as was done in this case.

The most interesting feature of this case was a recurrence of pneumothorax on the same side approximately six weeks after complete healing of the pneumothorax. Although the second attack of pneumothorax was a moderately severe one, the amount of fluid present was so small that aspiration was not attempted and the fluid quickly disappeared.

Snively et al.<sup>12</sup> state that there are no recorded cases of recurrent spontaneous hemopneumothorax. They state that pleural adhesions following the presence of blood in the pleural cavity make further collapse impossible. Hopkins<sup>13</sup> also states that there are no recorded cases of recurrent hemopneumothorax. He states that the fibrin deposits, or the presence of blood in the pleural cavity, with the resulting sterile pleurisy, lead eventually to the formation of such extensive pleural adhesions that subsequent collapse and bleeding become impossible.

We found that Rist<sup>14</sup> had recently reported a case of spontaneous hemopneumothorax which was followed two years later by a spontaneous pneumothorax on the same side. In this case, however, there was only a small amount of hemorrhagic fluid present originally. Repetti<sup>15</sup> reported a case with a rather large hemorrhagic effusion which showed a recurrent attack of hemopneumothorax 87 days after the first attack. We believe that ours is the first reported case in the American literature of a large spontaneous hemopneumothorax which was followed by a recurrence on the same side.

### SUMMARY

A case of spontaneous pneumothorax in a 51 year old male with previously unrecognized congenital cystic disease of the lung is reported. The removal of a large amount of air and the injection of the patient's own blood into the pleural cavity resulted in a rapid clinical cure.

A case of complete atelectasis of the upper lobe of the left lung associated with a spontaneous pneumothorax is recorded. Pneumothorax had been present for 11 months. The collapsed lung rapidly reexpanded following bronchoscopy, and there was no evidence of disease in the lung following reexpansion. A careful survey of the literature shows only one previous report of atelectasis following idiopathic spontaneous pneumothorax.

A case of spontaneous hemopneumothorax with recovery followed by a recurrence of the pneumothorax is recorded. This is the third reported case of recurrence of pneumothorax following spontaneous idiopathic hemopneumothorax. It has frequently been stated that adhesions follow hemopneumothorax and prevent recurrence.

## BIBLIOGRAPHY

1. SCHENCK, S. G.: *Diagnosis of congenital cystic disease of the lung*, Arch. Int. Med., 1939, ix, 1-21.
2. SHENK, S. G.: *Congenital cystic disease of the lungs*, Am. Jr. Roentgenol., 1935, xxxv, 604-629.
3. SOKOLOFF, M. J., and FARRELL, J. T., JR.: *Spontaneous pneumothorax in anthro-silicosis*, Jr. Am. Med. Assoc., 1939, cxii, 1564-1566.
4. WATSON, E. E., and ROBERTSON, C.: *Recurrent spontaneous pneumothorax: report of three cases*, Arch. Surg., 1928, xvi, 431.
5. HENNEL, H., and STEINBERG, M. F.: *Tense pneumothorax: treatment of chronic and recurrent forms by induction of chemical pleuritis*, Arch. Int. Med., 1939, lxiii, 648-663.
6. Unreported Cases.
7. KJAERGAARD, H.: *Spontaneous pneumothorax in the apparently healthy*, Acta med. Scandinav., supp. 43, 1931, 1-159.
8. PALOCIO, J., and MAZZEI, E. S.: *Die Atelektase beim Spontanpneumothorax*, Schweiz. med. Wchnschr., 1941, lxxi, 601-602.
9. ESCUDERO, L., and ADAMS, W. E.: *Spontaneous pneumothorax associated with massive atelectasis, an experimental and clinical study*, Arch. Int. Med., 1939, lxiii, 29-38.
10. SANTE, L. R.: *Massive (atelectatic) collapse of the lung with report of a case showing associated spontaneous pneumothorax*, Am. Jr. Roentgenol., 1928, xx, 213-217.
11. HARTZELL, H.: *Spontaneous hemopneumothorax, report of 3 cases and review of literature*, Ann. Int. Med., 1942, xvii, 496.
12. SNIVELY, D., SHAUMAN, H., and SNIVELY, W. D.: *Spontaneous hemopneumothorax, report of a case*, Ann. Int. Med., 1942, xvi, 349-356.
13. HOPKINS, H. U.: *Spontaneous hemopneumothorax: report of 3 cases with a review of the literature*, Am. Jr. Med. Sci., 1937, cxcii, 763-772.
14. RIST, E., and WORMS, R.: *Sur un cas d'hémopneumothorax spontané*, Bull. et. mém. Soc. méd. d. hôp. de Paris, 1940, lvi, 272.
15. REPETTI, L. P.: *Secuelas del hemoneumothorax Espontaneo*, Semana méd., 1940, ii, 1186-1190.

# LUPUS ERYTHEMATOSUS (ERYTHEMATODES) AND OVARIAN FUNCTION: OBSERVATIONS ON A POSSIBLE RELATIONSHIP, WITH REPORT OF SIX CASES\*

By EDWARD ROSE, M.D., F.A.C.P., and DONALD M. PILLSBURY, Colonel,  
M.C., A.U.S., *Philadelphia, Pennsylvania*

THE syndrome which is unfortunately known as lupus erythematosus has been the subject of an enormous literature since Hebra's clinical description, under the name of *seborrhea congestiva*, in 1845. The primary etiology and pathogenesis of the disease still remain elusive despite the development of several theories.<sup>1</sup> The use of the term "lupus" was introduced in the latter part of the nineteenth century when the disease was generally considered to be tuberculous. Although opinion is still somewhat divided, a tuberculous etiology has not been established. The term "lupus," therefore, must be regarded as a misnomer, although its use has by this time become so entrenched by custom that abandonment of it may be difficult. Substitution of the term "erythematoses" as suggested by Jadassohn and others<sup>2</sup> would nevertheless appear desirable.

The morbid anatomy, both cutaneous and visceral, as well as the clinical features of the erythematoses syndrome have been thoroughly described.<sup>3</sup> Among the several suggested classifications, that proposed by Urbach and Thomas<sup>4</sup> appears to be simplest and most practical.

Their classification is as follows:

Chronic	{ discoid disseminated
Exacerbated	{ discoid disseminated
Genuine acute (systemic)	{ acute subacute

In the chronic discoid type the cutaneous lesions are usually limited to the cheeks, nose and hands, with occasional involvement of the scalp, forehead, ears and lower anterior neck. The lesions are sharply circumscribed, elevated and reddish in color with frequent silvery scaling beneath which keratotic plugs often extend into hair follicles and the mouths of sebaceous glands. The lesions may remain indolent for many years or they may grow slowly by

\* Received for publication July 20, 1944.

From the Endocrine Section of the Medical Clinic and the Department of Cutaneous Medicine, Hospital of the University of Pennsylvania.

Colonel Pillsbury's contribution to this communication preceded his entry into the Army of the United States.

peripheral extension, while central atrophy and scarring develop. Systemic manifestations are uncommon and mild, consisting of occasional slight fever, mild anemia or leukopenia, fatigability and malaise. The chronic disseminated form differs from the discoid chiefly in the widespread distribution of the lesions and in their tendency to increase in size by confluence. The prognosis of these chronic forms is relatively benign and the incidence of improvement or cure has been reported as high as 60 per cent.<sup>6</sup> Females are affected somewhat more often than males (52 to 67 per cent females) and the disease appears most often in young or middle-aged persons. Acute or subacute systemic manifestations occasionally appear.

In the exacerbated forms of discoid or disseminated erythematodes acute inflammatory changes may appear in the erythematous lesions, which may increase rapidly in size and number. In addition, a variety of polymorphic lesions may be seen in the skin and mucous membranes, including bullous, necrotic, ulcerative, crusted, hemorrhagic, papular and pellagroid changes. Such exacerbations may occur without apparent cause or they may follow the removal of focal infection, exposure to cold, ultraviolet or actinic irradiation, burns, trauma, or treatment with gold, bismuth, quinine or carbon dioxide snow. In addition, acute or subacute systemic manifestations may occur. These include fever of irregular type, arthralgia, adenopathy, anemia, leukopenia, thrombocytopenia, splenomegaly, pleurisy, pericarditis and peritonitis with effusion, bronchopneumonia, endocarditis, meningitis, acute ulceration of the gastrointestinal tract and vascular lesions in the retina sometimes accompanied by papilledema. Renal lesions of varying character are likewise common with the urinary excretion of albumin, casts and abnormal numbers of red and white blood cells.<sup>6</sup> The constancy and specificity of the renal lesions, particularly those affecting the glomeruli, are still subject to some differences of opinion<sup>7</sup>; in our experience, however, glomerular damage and terminal renal failure have been strikingly frequent. The endocardial vegetations and myocardial changes have been thoroughly described.<sup>8</sup> Many authorities believe that the atypical verrucous endocarditis described by Libman and Sachs<sup>9</sup> occurs as a variant of, or as a part of the clinical picture in systemic erythematodes. During systemic exacerbations as well as in the chronic phases of the disease pathogenic microorganisms cannot as a rule be recovered from the blood stream. Occasionally, however, one or more of several varieties of pathogens (pneumococci, streptococci, etc.) appear in blood cultures, probably as secondary or terminal invaders.

In the group described by Urbach and Thomas<sup>4</sup> as the genuine acute form, systemic manifestations appear shortly after, or sometimes even before, the onset of the cutaneous lesions. The latter are usually florid, and the systemic manifestations often develop with explosive violence. The entire course of the disease may occupy only a few weeks or months. Occasionally in the so-called subacute variety of this genuine acute form several exacerbations and remissions may be seen. In all types of erythematodes a history

of marked sensitivity to light is common, and violent exacerbations may follow exposure. The prognosis in acute exacerbated, and in the genuine acute forms is very grave, the mortality having been estimated<sup>10</sup> as high as 100 per cent. Occasionally, however, a surprising remission may occur in patients appearing almost moribund. In the subacute systemic types the mortality rate has been estimated at about 50 per cent.<sup>10</sup> The cause of death in systemic erythematodes may be renal failure, bronchopneumonia, meningitis, secondary sepsis, or hyperpyrexia with exhaustion.

The nature of the basic pathological process remains the subject of disagreement. Because of the protean characteristics of the disease and the ubiquitous distribution of its lesions, it has been thought that the fundamental abnormality resides in the vascular system, and the term "visceral angiitis" has been offered as a synonym.<sup>9</sup> As a further refinement the collagen elements of connective tissue have been suggested as the primary locus, and the term "diffuse collagen disease" has been proposed.<sup>11</sup>

The pathogenesis of erythematodes remains obscure. The possible importance of photosensitivity has been mentioned, and in this connection the rôle of porphyrins, particularly those produced in the intestinal tract, has received considerable attention.<sup>12</sup> The importance of infectious-allergic and vasculo-allergic factors has recently been thoroughly considered by Stokes, Beerman and Ingraham.<sup>1</sup> Focal infection, tuberculosis and even lead poisoning have likewise been suggested but without convincing proof. The high mortality in the acute and subacute systemic exacerbations indicates the ineffectiveness of present therapy. A variety of therapeutic agents have been about equally futile; these include sulfonamides, transfusions of whole blood and plasma, vitamins, liver extract, general supportive measures and a number of purportedly specific drugs.

From the foregoing it will be apparent that erythematodes constitutes a syndrome of obscure etiology and pathogenesis in which widespread systemic involvement frequently appears as a grave complication. It is also apparent that no effective therapy has yet been found for the prevention or control of these systemic exacerbations, and that further search for more effective therapeutic measures is necessary. In our experience with the disease *we have been impressed by the striking frequency with which systemic involvement occurs in females during the active sexual phase of life* (i.e., between puberty and the menopause). Systemic exacerbations affect females from three to four times as often as males.<sup>13</sup>

Between January 1930 and May 1944 we have encountered 29 patients presenting evidence of erythematodes with acute or subacute systemic manifestations. Statistical data relating to these patients are shown in tables 1 and 2. From these tables it will be seen that females predominated by more than three to one, and in the genuine acute group by almost six to one. It is also apparent that 21 of the 22 females were in active menstrual life at the time of onset of their disease, and that most of them were below the

TABLE I

Types		Known Dead	Known Living	Fate Uncertain
Acute exacerbated	11 {Female.....	4	3	2
	Male.....	1	1	0
Genuine acute	13 {Female.....	11	0	0
	Male.....	2	0	0
Genuine subacute	2 {Female.....	1	0	0
	Male.....	1	0	0
Uncertain classification	3 {Female.....	0	1	0
	Male.....	0	1	1
Totals	29 {Female (22).....	16	4	2
	Male (7).....	4	2	1

TABLE II

Age of Onset	Females	Males
10-19	7	0
20-29	12	2
30-39	2	4
40-49	0	1
50-59	0	0
60-69	1	0

age of 30. Our data also emphasize the extremely grave prognosis in the genuine acute type of exacerbation, all of the 13 patients in this group having died. The possible relationship of ovarian function to these types of erythematodes is further suggested by the premenstrual accentuation of chronic discoid and disseminated skin lesions reported by some patients.

Because of the striking sex incidence of the disease and the ineffectiveness of other methods of therapy we were led to employ as early as 1939 large daily intramuscular injections of testosterone propionate (25 mg.) in six acute and subacute cases.\* The results were inconclusive. We then conceived the idea of destroying ovarian function, either by irradiation or by oöphorectomy in selected cases of erythematodes. In June 1942 the first of a group of five patients was castrated by oöphorectomy. We later learned that the treatment of erythematodes in the female by castration had previously been reported by others. Contratto and Levene<sup>15</sup> in 1939 reported a case of erythematodes in which irradiation of the ovaries was tried, the patient unfortunately dying of pneumonia before the effects of treatment could be evaluated. Sosman and his associates<sup>16</sup> have employed similar therapy in several other cases but without striking results. Cluxton and Krause<sup>17</sup> have recently mentioned suppression of ovarian function as a possibly useful therapeutic procedure in erythematodes with systemic manifestations. We report below six cases in which the course of the disease was observed following a spontaneous or artificial menopause.

\* This therapeutic agent has also been suggested by Baehr.<sup>14</sup>

## CASE REPORTS

*Case 1.* D. G., a white unmarried woman, aged 25, was first admitted to the service of Dr. John H. Stokes at the Hospital of the University of Pennsylvania on September 3, 1938. An eruption had appeared on the cheeks and nose three years previously. This had become steadily worse in the last two years, especially so after a course of irradiation and injections of gold and bismuth four months prior to admission. Afternoon fever and malaise had been noted for several months. In 1936 she had been treated for salpingo-oöphoritis, with surgical drainage of the cul-de-sac. There had been occasional nose bleeds and joint pains since 1934. There was a strong family history of tuberculosis. Examination showed typical erythematous macular lesions of erythematodes on both cheeks, the bridge of the nose and the left ear, with a number of small macular lesions, ascribed to mosquito bites, scattered over the extremities. The tonsils and one molar tooth were infected, and there was evidence of chronic infection in the urethra, cervix and Fallopian tubes. Cervical adenopathy was present. There was a regular, moderate afternoon fever, not exceeding 100° F. There was slight anemia and leukopenia, with a moderate increase in the sedimentation rate of the erythrocytes. Hemolytic *Staphylococcus aureus* was cultured from the urine. An intracutaneous tuberculin test was positive with 0.001 mg. O. T. Roentgenograms of the chest showed a healed primary complex in the right lung. The pelvic infection received local treatment and the infected tooth and tonsils were removed. The patient improved and was discharged on November 6, 1938.

During the following year the facial lesions varied in intensity and several new erythematous plaques appeared on the right cheek. Her treatment included several series of injections of bismuth and gold salts and sulfonamides. In November 1939 weakness and malaise increased and low grade fever with occasional chills was noted. The patient was readmitted to the hospital November 29, 1939. At this time the skin lesions had extended to both ears and the right supraorbital region. There was widespread adenopathy, and prominence of the superficial veins was noted over the neck and thighs. Evidence of pelvic infection was still present in addition to cystitis and left-sided pyelitis. Moderate anemia, leukopenia and increased sedimentation rate of the erythrocytes were still present. The patient remained in the hospital until July 4, 1940. During this time there were repeated exacerbations and remissions affecting both the cutaneous lesions and her general condition with irregular fever most of the time. Treatment included sulfanilamide, the injection of autogenous vaccines and estrogens, urinary antiseptics, dilatation of the left ureter by catheter and finally testosterone propionate. Estrogen therapy seemed to make the erythematodes worse, and severe general reactions followed each ureteral dilatation, so that these measures were soon abandoned. Within two weeks after institution of testosterone therapy, marked general improvement occurred and the patient was in complete remission when discharged July 4, 1940.

In August 1940 and again in January 1941 she suffered attacks of otitis media, the last one associated with "grippe." In September 1940, tender erythematous areas appeared on the forearms. In March 1942, there was lumbar backache and urinary frequency. The facial lesions remained quiescent until March 1942 when there was a marked increase in redness and swelling. She was readmitted to the hospital April 14, 1942, for consideration of castration. At this time the cutaneous lesions on the face and ears were florid and lesions were present on the arms which closely resembled tuberculids. There was slight enlargement of the spleen and liver, cervical adenopathy, anemia, leukopenia, and increased sedimentation rate of the erythrocytes. Infection of the left kidney and bladder was still present. Roentgenograms of the chest now showed bilateral apical lesions presumably tuberculous. No tubercle bacilli, however, could ever be found in the sputum. A tender mass was palpable in the left adnexa. On June 1, 1942, under spinal anesthesia, the uterus, both ovaries and tubes

were removed. The specimens showed chronic oöphoritis and salpingitis but no histological evidence of tuberculosis. Her postoperative convalescence was uneventful except for an acute exacerbation of pyelocystitis which soon responded to urinary antiseptics. The cutaneous lesions began to improve within two weeks after the operation and by August 1942 all evidence of activity had disappeared leaving only scarring.

The patient has been seen regularly at intervals of three months since operation. Except for occasional migrainous headaches, hot flashes, and one or two acute episodes of lumbar backache she has remained entirely well. She has gained 25 pounds and has been regularly employed in a shell loading plant. In November 1942 she was briefly exposed to intense light from a burning signal flare and for a few weeks thereafter there was a slight recurrence of erythema on the left cheek. With this exception the cutaneous lesions have remained entirely in abeyance. Repeated roentgenograms of the lungs have shown no significant change in the apical lesions. Moderate left cervical adenopathy is still present with calcification in some of the nodes. At the time of her last examination (April 25, 1944) there was moderate anemia and a slight increase in the sedimentation rate of the erythrocytes. Her temperature has not exceeded 99° F. at any examination since her last discharge from the hospital.

Comment. This 25 year old white woman presented the picture of recurrent acute and subacute exacerbations of chronic discoid (disseminated?) erythematoses with moderate evidence of systemic involvement. Her disease was complicated by infection in the urinary tract, pelvic organs, teeth and tonsils and by probable pulmonary tuberculosis. Some of the cutaneous lesions on the extremities may have been tuberculids. After an irregular course, without substantial improvement, extending over almost six years she has shown very striking improvement with practically complete disappearance of cutaneous lesions as well as a marked gain in general health following the removal of her uterus, tubes and ovaries. So far as we are aware this is the first reported instance in which surgical castration has been performed as part of the treatment of erythematoses. The possible importance of the salpingitis, as well as of the urinary tract infection, in maintaining the activity of the erythematoses cannot be overlooked. We must admit the possibility that the removal of the Fallopian tubes, and the subsidence of the urinary tract infection, may have been important factors in this patient's improvement. It is interesting to note that her improvement has been maintained despite the absence of significant change in the roentgenographic appearance of the pulmonary lesions.

Case 2. In 1934, V. A., an unmarried colored woman, at the age of 35 began to notice intermittent pallor and blueness of the right third and fourth toes associated with spasmodic pain on walking; several small hemorrhagic areas were noted soon afterward on the affected toes. She remained well after the subsidence of these symptoms until the winter of 1935-1936, when cramp-like pains were noted during sleep in the calves of both legs. Shortly afterward intermittent pain, pallor, mottling, redness and cyanosis of the fingers appeared. These symptoms were more marked in moderate than in cold temperatures, and were alleviated during menses. In March 1937 there was abrupt onset of diarrhea, anorexia, fatigue and pain in the left shoulder followed by cramp-like epigastric pain. She was admitted to the New Haven Hospital where examination showed fever, abdominal distention, and essentially normal blood count, and roentgenographic evidence of left ventricular enlargement and infiltration in the left lower lung. The signs and symptoms subsided promptly and she was discharged after three days. One month later numbness and pain appeared in the fingers with redness and ecchymotic spots over the distal phalanges. On July 6, 1937, she was first admitted to the Hospital of the University of Pennsylvania under the care of Dr. E. M. Landis. The principal findings included moderate irregular fever, abdominal distention with epigastric pain and



tenderness, and slight enlargement of liver and spleen; the heart was overactive and slightly enlarged to percussion, with a loud blowing systolic murmur audible over the entire precordium and transmitted into the left axilla. Movement of the right diaphragm was limited. The right dorsalis pedis pulse could not be felt. Several reddish nodules were scattered over the anterior surface of both lower legs and there were a few splinter hemorrhages under the fingernails. Several elevated erythematous plaques were scattered over the cheeks and lower thighs. The sedimentation rate of the erythrocytes was increased to 35 mm. per hour. There was moderate anemia (hemoglobin 49-78 per cent) and leukopenia (leukocytes 5700 to 9000 per cu. mm.). Platelet counts were normal. Blood cultures remained sterile, but *Streptococcus mitis* was recovered from the urine. No foci of infection could be found in the upper respiratory tract, teeth, pelvis or gastrointestinal tract. Signs and symptoms gradually subsided and the patient was discharged still showing quiescent erythematous facial lesions, with a tentative diagnosis of lupus erythematosus with acute systemic manifestations.

During the winter of 1937-1938 the facial lesions fluctuated in intensity and several new erythematous lesions appeared on the hands and legs. Showers of petechiae appeared occasionally on the extremities and abdomen and on at least one occasion these were associated with symptoms suggesting hemorrhage or infarction in the spleen and left lung. The patient was easily tired, slightly anemic and often mildly febrile. Her menses became increasingly profuse. On August 11, 1938, a supravaginal hysterectomy was performed by the late Dr. P. B. Bland at the Jefferson Hospital because of a fibroid tumor of the uterus. The ovaries were not removed. A postoperative pulmonary complication was reported as the result of embolism.

During the following winter the patient remained in fair health although continuing somewhat anemic and with intermittent painful dusky lesions on the fingers. No fresh skin lesions were noted until January 1942 when some scaling and extension of the facial lesions were observed. In March 1942 the patient was readmitted to the Hospital of the University of Pennsylvania with streptococcal bronchopneumonia and hemolytic streptococcic bacteremia. At this time there was some anemia, leukopenia and thrombocytopenia (platelets 80,000 per cu. mm.). Fresh disseminated erythematous and bullous lesions appeared on the face, lips, ears, scalp and extremities. The patient was desperately ill for several days but improved gradually following the use of sulfadiazine, testosterone and blood transfusions.

Irregular menstrual bleeding had continued after the hysterectomy. In the summer of 1942 hot flashes and sweats appeared and the menstrual bleeding became scantier and less frequent. Coincidentally with these menopausal manifestations there was marked improvement both in the appearance of the cutaneous lesions and in the patient's general health. Since that time she has been able to continue her work as a physician with few interruptions, and no severe exacerbations have appeared. She has remained mildly anemic with occasional febrile episodes and from time to time there have been scattered, painful petechiae and tender erythematous nodules over the lower anterior legs. The facial lesions, however, have remained quiescent. Because occasional slight vaginal bleeding still recurred at irregular intervals irradiation of the ovaries was advised in October 1943 for the purpose of suppressing menstruation permanently. Because of the demands of her professional work the patient was unable to follow this suggestion. Her last menstrual bleeding occurred January 1944.

Comment. This negro woman, now 45 years old, has survived seven years of repeated acute and subacute systemic exacerbations of disseminated erythematodes. The onset of recognizable cutaneous lesions was preceded by three years of vague ill

health associated with peripheral vasomotor signs and symptoms, somewhat simulating Raynaud's disease. Petechial and nodose erythematous lesions have been prominent. General improvement appeared coincidentally with the manifestations of a natural menopause.

*Case 3.* M. V., a 26 year old white married woman, had received treatment intermittently since 1936 for discoid erythematodes involving the cheeks, nose and ears. She frequently noted a premenstrual intensification of the erythematous lesions. In 1941 she was treated for an acute illness which was diagnosed as rheumatic fever; a younger brother had had an attack of rheumatic fever also. In the summer of 1942 she began to lose weight and during the following year her weight fell from 125 to 86 pounds. In May 1943 she noted pain and swelling in the left ankle. This was followed by fugaceous pain in various other joints, "pleuritic" pains in the chest, epigastric distress, palpitation, anorexia, malaise and fever. There was, however, no increase in the severity of the cutaneous lesions during this time. On August 14, 1943, she was admitted to the Delaware Hospital in Wilmington, Delaware, under the care of Dr. Edgar Miller, where she remained until October 16, 1943. During this time the cutaneous lesions remained quiescent but there was irregular fever up to 102° F. until September 19, after which time her temperature remained virtually normal. The patient was cachectic and weak with typical lesions of discoid erythematodes involving the cheeks, nose and ears. There was bilateral cervical adenopathy. The heart was markedly enlarged with a moderately loud apical systolic murmur and an occasional presystolic gallop. The rate was rapid much of the time. A transitory pericardial friction rub persisted for about five days. A moderate left pleural effusion appeared, but did not recur after the second aspiration. The liver was slightly enlarged but the spleen could not be palpated. Both eyes showed marked chorio-retinal vascular degeneration and optic neuritis with papilledema; these lesions progressed steadily and vision was eventually lost. Moderate hypertension was present most of the time, the systolic pressure varying from 125 to 180 mm. Hg and the diastolic from 80 to 120 mm.

The principal laboratory findings included a moderate fixed reduction in the specific gravity of the urine, with the excretion of varying amounts of albumin, hyaline and granular casts, and the occasional presence of erythrocytes. The sedimentation rate of the erythrocytes was increased to 30 mm. per hour. There was moderate anemia, the hemoglobin varying from 60 to 80 per cent, and the red cells from 3.1 to 4 million; the leukocyte counts varied from 6,100 to 14,200. The blood urea nitrogen ranged from 9 to 22 mg. per 100 c.c. The total serum protein varied from 5.0 to 7.9 gm. per cent. Blood Wassermann and Kahn reactions were negative. Three blood cultures remained sterile.

Except for a reaction following a blood transfusion on August 23 the patient's condition remained essentially unchanged until her temperature returned to normal on September 19. From this time until her discharge October 16, she remained afebrile, and her strength and appetite gradually improved. Her hypertension persisted, however, and her vision deteriorated. She was seen in consultation by one of us (E. R.) on September 12, at which time therapeutic castration was suggested, despite the fact that she had not menstruated since June 1943. Oöphorectomy was not considered justifiable because of her poor general condition. Therefore, irradiation of the ovaries was employed, and a menopausal dose was given in five installments between September 18 and 27. Following her discharge from the hospital, evidence of progressive renal failure soon appeared and death occurred as a result of uremia two months later.

*Comment.* This 26 year old woman gave a history of premenstrual local exacerbations of discoid erythematodes for several years, followed by a subacute systemic exacerbation without corresponding intensification of the cutaneous lesions.

Pericardial, pleural and renal involvement dominated the systemic syndrome. The renal damage which caused her death was probably well advanced by the time irradiation of the ovaries was begun.

*Case 4.* J. F., a white unmarried woman, aged 24, was admitted to the Hospital of the University of Pennsylvania under the care of Dr. B. I. Comroe on January 11, 1943, and remained until January 20, 1943. Since 1940 she had complained intermittently of malaise, fatigue, occasional slight fever and migratory arthralgia. In June 1942 an erythematous facial eruption had appeared following prolonged exposure to the sun. This had persisted with varying intensity, and a diagnosis of lupus erythematosus had been made. Acute painful swelling of the right upper eyelid with conjunctival injection occurred on two occasions. In December 1942 she suffered an acute attack of left-sided pleurisy, following which low grade fever had persisted and arthralgia had recurred. On admission she complained of pain and stiffness involving the ankles, knees, elbows, toes and fingers. Examination showed typical lesions of erythematodes involving the cheeks and nose. There was slight fever, evidence of moderate weight loss, cervical and axillary adenopathy, a left-sided pleural effusion and a systolic murmur over the base of the heart. The blood pressure varied from 120 mm. Hg systolic and 80 mm. diastolic to 140 mm. systolic and 90 mm. diastolic. The urine contained varying amounts of albumin and moderate numbers of leukocytes; culture of the urine yielded hemolytic *Staphylococcus albus*. The hemoglobin varied from 73 to 80 per cent, the leukocyte count from 5,500 to 7,800 per cu. mm. The blood uric acid was slightly increased (4.9 mg. per 100 c.c.) The blood urea nitrogen was 9 mg. per 100 c.c. The urea clearance was normal (90 per cent of average normal function), but the phenol-sulphonephthalein excretion was reduced to 34 per cent in two hours. Intravenous urography with Diodrast showed evidence of impaired tubular function. The pleural effusion on aspiration was found to be bacteriologically negative.

The diagnosis of erythematodes with systemic involvement was confirmed by Dr. John H. Stokes. Surgical castration was advised but was declined by the patient's father, who was a physician. Ovarian irradiation was accepted, and this therapy was carried out between February 24 and March 11, 1,000 r units being delivered to each ovary. The patient's menses, previously normal, recurred only once after irradiation.

She was readmitted to the hospital June 13, 1943. During the interval there had been definite recession of the facial lesions, but her general condition had not improved. There were intermittent fever, fluctuating hepatomegaly, recurrence of the pleural effusion, and progressive anemia. Marked albuminuria was almost constant and large numbers of casts, leukocytes and erythrocytes continued to appear in the urine. On readmission there was generalized edema, with bilateral pleural effusion, severe anemia without leukocytosis (hemoglobin 59 per cent, leukocytes 5,900 per cu. mm.), and a temperature of 103° F. The blood urea nitrogen had risen to 70 mg. per 100 c.c., and the serum protein was 5 gm. per cent. Several blood transfusions and general supportive treatment proved unavailing and she was discharged June 19 unimproved. She died at home of renal failure on July 6, 1943.

*Comment.* This 24 year old patient first developed the cutaneous lesions of erythematodes after two years of vague ill health and intermittent fever with migratory arthralgia. Systemic involvement became manifest six months later, and her clinical course was marked by progressive renal damage which was the principal cause of her death. As in case 3, it seems probable that renal damage was well advanced by the time ovarian irradiation was begun.

*Case 5.* V. H., a white married woman, aged 37, was first seen April 6, 1943. She had received treatment intermittently by local irradiation and various other means during the preceding five years for discoid erythematodes limited to the face and forehead. There had never been any evidence of systemic involvement. Her

menses had always been normal, and there had been no premenstrual aggravation of the cutaneous lesions. Except for the erythematodes and bilateral cervical adenopathy, physical examination was negative. There was slight leukopenia (leukocytes 5,500 per cu. mm.), but no anemia or thrombocytopenia. The sedimentation rate of the erythrocytes was slightly increased. A menopausal dose of irradiation was delivered to the ovaries in April, after which she menstruated only once. Menopausal symptoms of moderate severity followed. The last report from the patient was received November 3, 1943, at which time she stated that there had been no change in the appearance of the cutaneous lesions.

*Case 6.* M. F., a white married woman, aged 40, had suffered her first outbreak of erythematodes on the face and neck soon after the birth of her first child at the age of 26. The lesions subsided after two years of local treatment but recurred after the birth of her second child at the age of 32. Since that time the erythematous lesions had remained intermittently active with regular premenstrual exacerbations. There had never been any evidence of systemic involvement. Her menstrual periods had always been regular, but became increasingly profuse and at the age of 35 the right ovary and tube were removed. Following this operation the menses became less profuse but continued regular, and the premenstrual cutaneous exacerbations persisted. Various local methods of treatment had been of no avail. Physical examination showed characteristic erythematodes involving the face and neck with bilateral posterior cervical adenopathy. The blood count was not remarkable. Roentgenograms of the lungs showed a calcified lesion in the right upper lobe. There was no evidence of systemic involvement. A menopausal dose of irradiation was delivered to the left ovary in February 1943 after which menstruation ceased. The cutaneous lesions improved markedly until September 1943. At this time a moderate exacerbation accompanied by slight fever followed an acute pharyngitis. The exhibition of small doses of sulfadiazine was followed by a remission. The erythematodes remained quiescent until January 1944 when another flare-up followed the appearance of two dental abscesses. Since that time the cutaneous lesions have shown recurrent activity but no systemic manifestations have appeared.

### DISCUSSION

It is obvious that the cases described above present neither proof of a relationship between ovarian function and erythematodes, nor clear-cut evidence of the efficacy of castration in controlling the disease. The most striking results were observed in case 1, but in this patient the coincidental removal of pelvic infection may well have been an important factor. In case 2, definite improvement, but not complete remission, followed a natural menopause. In cases 3 and 4, the renal lesion which ultimately caused death was probably well initiated before castration was undertaken, and in that respect may not have presented a fair trial for the procedure. Even though definite proof of a relationship between ovarian function and erythematodes could be established, it would not necessarily follow that the ovarian hormones constituted the only, or even a major, etiologic factor. Stokes, Beerman and Ingraham<sup>1</sup> have emphasized the importance of infectious-allergic and vasculo-allergic factors in the pathogenesis of erythematodes. They mention the possible importance of gonadal hormones and "menotoxins" in contributing to cutaneous vasodilatation and thus perhaps increasing cutaneous sensitivity to actinic irradiation as well as infectious and other

allergens. It is conceivable that ovarian hormones might act as sensitizing agents, that they might produce cutaneous vasodilatation, or that they might play an intermediate part in the production of a toxic agent.

Since the lesions of erythematodes have so far not been reproducible in lower animals, the experimental approach to an understanding of its etiology and pathogenesis has not been possible. Further evidence relating to a possible rôle of gonadal function might be obtained by the following methods: (a) determination of the androgen-estrogen ratio, the urinary excretion of 17-ketosteroids, and the urinary excretion of pituitary gonadotropic hormones in patients of both sexes during exacerbations and remissions; (b) a statistical study, in a numerically significant group of cases, of the effect of castration in preventing systemic exacerbations, compared with a control group; (c) histologic study and correlation of changes found in the gonads and other endocrine organs of patients with erythematodes coming to necropsy; (d) production or reproduction of systemic exacerbations by the administration of gonadal steroid hormones. Some of these procedures would appear to be ethically unjustifiable at present. At best, the collection of significant data by any of these methods would be handicapped by the relative infrequency with which systemic manifestations of the disease are encountered.

The demonstration of a decreased androgen-estrogen ratio, or an increase in pituitary gonadotropin production in males with systemic involvement might be considered as evidence supporting the rôle of estrogens in the pathogenesis of erythematodes. We have had an opportunity to measure the urinary 17-ketosteroids, gonadotropic and estrogenic substances in a 26 year old male, during an acute systemic exacerbation of the disease. There was no clinical evidence of gonadal or other endocrine dysfunction. The urine contained 7.52 mg. of true 17-ketosteroids per 24 hours (normal 10 to 19 mg. per 24 hours), 100 to 150 mouse units of estrogen, and 50 mouse units of gonadotropin in 24 hours by uterine weight assay (50 to 75 m.u. by vaginal smear, and less than 10 m.u. by ovarian weight). These estrogen levels are well within the normal range for adult males and the gonadotropin as measured by uterine weight responds to somewhat above the usual normal for males. These findings indicate a probable reduction in androgen-estrogen ratio with an increase in gonadotropic pituitary activity. The observations of Selye and others<sup>18</sup> upon the experimental production of renal lesions, followed by hypertension, after the administration of adreno-cortical steroids are of interest in view of the frequency of glomerular lesions and hypertension in erythematodes. In this connection physiologic resemblances of progesterone to the adrenocortical steroids come to mind.

If it be granted that a reasonable argument exists for a further trial of so radical a procedure as castration of the female in an effort to prevent or control systemic exacerbations in erythematodes, the technic and timing of

the procedure require consideration. Oöphorectomy would appear the surest method of eliminating permanently all ovarian hormones, provided the surgical risk appears justifiable in a given case. Menopausal doses of irradiation probably do not suppress ovarian function immediately, and most patients menstruate at least once after the completion of such therapy. The danger of provoking or aggravating systemic involvement by irradiation of the pelvic area would not appear to be great enough to contraindicate the procedure. In genuine acute or subacute exacerbations, in which the systemic phenomena appear coincidentally with, or soon after, the cutaneous lesions, the patient is usually so sick that laparotomy presents too grave a hazard to be justifiable. The optimal indications for castration would appear to be (a) in women with a history of premenstrual aggravation of the cutaneous lesions, and with mild systemic phenomena (slight fever, anemia, leukopenia, adenopathy, arthralgia, malaise, etc.) and (b) in women in active menstrual life who have shown one or more systemic exacerbations with intervening remissions. A period of remission would obviously appear to be the optimal time for castration.

In conclusion, it should be emphasized that the evidence which we have cited, although perhaps suggestive, is still far from proving that ovarian hormones play a part in the pathogenesis of erythematodes. Elective castration in a woman of child-bearing age or potentiality is a serious procedure, to be justified only if it offers some reasonable hope of improving an otherwise grave prognosis and then only with the full understanding of the patient. Nevertheless, it would appear from the evidence which we have discussed that further investigation of the possible relationship between the gonadal hormones and the pathogenesis of erythematodes is desirable. Our observations have been presented with the hope that they may stimulate such investigation.

#### SUMMARY

The clinical and pathological features of erythematodes (lupus erythematosus), and various theories relating to its pathogenesis have been briefly reviewed. Statistical data, collected from the literature and from 29 cases of our own, have been cited to illustrate (a) the striking frequency with which the systemic manifestations of erythematodes affect females within the active sexual phase of life; and (b) the failure of previous therapeutic measures.

The effects of castration or natural menopause upon the course of the disease have been described in six cases. Among these is the first patient known to us in whom oöphorectomy has been employed in the treatment of erythematodes. Measurements of urinary 17-ketosteroids, estrogens and gonadotropins in a male with erythematodes have been reported, which suggest a decreased 17-ketosteroid: estrogen ratio, and increased pituitary gonadotropic activity. The desirability of further investigation of gonadal function in the syndrome of erythematodes has been emphasized.

We are indebted to Drs. E. M. Landis, Edgar Miller, B. I. Comroe, E. P. Pendergrass, and Erich Urbach for permission to report Cases 2, 3, 4, 5 and 6, and to Dr. Olive Hoffman for performing the determinations of urinary 17-ketosteroids, estrogens and gonadotropins.

## BIBLIOGRAPHY

1. STOKES, J. H., BEERMAN, H., and INGRAHAM, N. R., JR.: The "lupus erythematosus" concept: an attempt at integration, *Am. Jr. Med. Sci.*, 1944, ccvii, 540.
2. JADASSOHN, J.: *Mracek's Handbuch der Hautkrankheiten*, 1904, iii, 319 (Quoted by Urbach and Thomas<sup>4</sup>).
3. (a) ROSE, E., and PILLSBURY, D. M.: Acute disseminated lupus erythematosus—a systemic disease, *Ann. Int. Med.*, 1939, xii, 951.  
(b) REIFENSTEIN, E. C., REIFENSTEIN, E. C., JR., and REIFENSTEIN, G. H.: A variable symptom complex of undetermined etiology with fatal termination, including conditions described as visceral erythema group (Osler), disseminated lupus erythematosus, atypical verrucous endocarditis (Libman-Sachs), fever of unknown origin (Christian), and diffuse peripheral vascular disease (Baehr and others), *Arch. Int. Med.*, 1939, lxiii, 553.  
(c) BANKS, B. M.: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosus, Libman-Sachs syndrome and polyarteritis nodosa? *New England Jr. Med.*, 1941, ccxxv, 433.
4. URBACH, E., and THOMAS, C. C.: Classification and definition of the clinical varieties of erythematoses (lupus erythematosus) with particular reference to its acute and subacute course, *Brit. Jr. Dermat.*, 1939, li, 343.
5. O'LEARY, P. A.: Symposium on lupus erythematosus, *Proc. Staff Meet. Mayo Clin.*, 1940, xv, 686.
6. KRUPP, M. A.: Urinary sediment in visceral angitis (periarteritis nodosa, lupus erythematosus, Libman-Sachs "disease"); quantitative studies, *Arch. Int. Med.*, 1943, lxxi, 54.
7. KEITH, N. M.: Symposium on lupus erythematosus, *Proc. Staff Meet. Mayo Clin.*, 1940, xv, 682.
8. GROSS, L., and FRIEDBERG, C. K.: Nonbacterial thrombotic endocarditis, classification and general description, *Arch. Int. Med.*, 1936, lviii, 620.
9. LIBMAN, E., and SACHS, B.: A hitherto undescribed form of valvular and mural endocarditis, *Trans. Assoc. Am. Phys.*, 1923, xxxviii, 46.
10. MONTGOMERY, H.: Symposium on lupus erythematosus, *Proc. Staff Meet. Mayo Clin.*, 1940, xv, 678.
11. KLEMPERER, P., POLLACK, A. D., and BAEHR, G.: Diffuse collagen disease; acute disseminated lupus erythematosus and diffuse scleroderma, *Jr. Am. Med. Assoc.*, 1942, cxix, 331.
12. URBACH, E.: Schwerste Lichtdermatosen auf Grundlage von isolierter pathologischer Porphyrinbildung im Darne infolge Dysbakterie und Hepatopathie, *Klin. Wchnschr.*, 1938, xvii, 304-310.
13. MATTRAS, A.: Zur Symptomatologie und Klinik tödlich verlaufender Fälle von Lupus erythematosus, *Arch. f. Dermat. u. Syph.*, 1938, clxxvii, 223.
14. BAEHR, G.: In *Text Book of Medicine* by R. S. CECIL, 1943, W. L. Saunders, Philadelphia and London, p. 461.
15. CONTRATTO, A. W., and LEVENE, S. A.: Acute lupus erythematosus disseminatus; report of case, *New England Jr. Med.*, 1939, ccxxi, 602.
16. SOSMAN, M.: Personal Communication.
17. CLUXTON, H. E., JR., and KRAUSE, L. A. M.: Acute lupus erythematosus disseminatus; *Ann. Int. Med.*, 1943, xix, 843.
18. SELYE, H.: Production of nephrosclerosis by overdosage with desoxycorticosterone acetate, *Canad. Med. Assoc. Jr.*, 1942, xlvii, 515.

# CASE REPORTS

---

## LIGATION OF PATENT DUCTUS ARTERIOSUS IN THE PRESENCE OF AN APPARENT BACTERIAL ENDOCARDITIS; REPORT OF CASE APPARENTLY CURED \*

By RALPH B. BETTMAN, M.D., and WILLIAM TANNENBAUM, M.D.,  
*Chicago, Illinois*

THE feasibility of ligation of a patent ductus arteriosus was first demonstrated by Gross.<sup>1</sup> The fact that ligation of a patent ductus arteriosus in the presence of what appears to be a bacterial endocarditis may result in the cure of the disease was definitely established by Touroff<sup>2</sup> and confirmed by several other reports.

However, inasmuch as medicine operates very much as law, on the basis of precedent, it will take an accumulation of statistics from many cases before the medical profession in general will become cognizant of this new therapeutic procedure. We, therefore, think it wise that for the next year or two we publish our results of ligation of patent ductus in the presence of bacterial endocarditis as these cases pass through our hands.

### CASE REPORT

F. Z., age 18, entered the hospital August 1942, with the history of chills, fever, and extreme malaise. Since early childhood she had had difficulty in breathing on exertion, and had been under observation in one of our Chicago clinics with the diagnosis of a congenital heart malformation, probably a patent ductus arteriosus. From the age of 10 she had attended the Spaulding school for invalid children where she got along well except for the dyspnea on exertion. As a baby she had "rheumatic fever," and in January 1942 had a "streptococcus infection of the lower lip." Except for the above mentioned conditions she had been in fairly good health until July 1942, when she suddenly became sick with a chill followed by high fever. Chills and fever had persisted a month, in spite of sulfathiazole treatment, before she was brought to Michael Reese Hospital. Here the diagnosis of bacterial endocarditis and a patent ductus arteriosus was confirmed and a ligation of the ductus advised. It was not until October, however, that the consent of her legal guardians could be obtained. During this stay in the hospital she ran irregular fever, at times as high as 105° F., with short intermissions of a day or two of nearly normal temperature.

Physical examination on admission to the hospital showed the following relevant findings. The patient was a sickly looking, pale-faced young girl lying listlessly in bed. She was despondent and remained so throughout her preoperative period. She was not cyanotic. When quiet in bed her respirations were normal and easy. She was dyspneic on exertion. There was a slight asymmetry of her chest, the left side

\* Received for publication January 28, 1943.

From the Surgical and Medical Services of Michael Reese Hospital.



being more prominent than the right. The heart was enlarged to the left on palpation and percussion. There was a loud systolic murmur, most pronounced over the pulmonic area, followed by a loud diastolic murmur transmitted down the left sternal border to the apex. There was a marked palpable thrill over the entire left chest. Capillary pulsation of lips and fingernails was observed. The spleen was palpable but not tender.

The blood pressure was the same in both arms, 120 mm. Hg systolic and 60 mm. diastolic. The first blood count showed 3,620,000 red blood cells, 10,550 white blood cells, 82 per cent polymorphonuclears, 11 per cent lymphocytes, 7 per cent monocytes, slight hypochromia, moderate anisocytosis, hemoglobin 72 per cent. Subsequent blood counts were surprisingly similar. Urinalysis and blood chemistry were approximately normal. Circulation time was not abnormal. Blood culture was positive for *Streptococcus viridans*. Roentgenographic examination of the chest showed an enlarged heart, a cardiothoracic ratio of 11.7/22.5, and increased convexity of the left heart border.

The electrocardiogram was inconclusive. Cardiac sound tracings confirmed the machinery murmur heard on auscultation.

On October 19, operation to ligate the ductus was undertaken. We followed the usual technic of an anterior incision into the left thoracic cavity, incising the mediastinal pleura over the aorta and demonstrating the arch of the aorta, the left pulmonary artery and the vagus nerve. The site at which the recurrent laryngeal nerve dips under the arch of the aorta marks the lateral border of the ductus arteriosus. The left pulmonary artery was greatly enlarged. The ductus arteriosus measured about 0.5 cm. from the pulmonary artery to the aorta and about 1.5 cm. in diameter. It is of interest to note that the palpable thrill accompanying each heart beat stopped the moment the ductus was compressed. In fact, had there been any doubt of the diagnosis of a patent ductus, it would have been immediately dispelled by this dramatic disappearance of the thrill. For anyone not familiar with the anatomy of this portion of the chest, the site at which the digital pressure can interrupt the thrill will be an excellent guide to the position of the ductus. Although there was a good deal of inflammatory reaction in the region of the root of the lung, we had very little difficulty in isolating the ductus and passing two ligatures of heavy braided silk around it. Before tying the ligatures they were pulled taut and the patient carefully observed lest because of some other unsuspected abnormality ligation of the ductus might not be tolerated. As soon as the ductus was shut off the thrill stopped, but otherwise there seemed to be no change in the patient's condition, and the blood pressure was essentially unchanged. The ligatures were now tied, one as close to the pulmonary artery, the other as close to the aorta as possible. The chest was closed without drainage. The procedure was much simpler than it would appear to have been from the above description; the entire procedure took less than an hour from the beginning of the anesthesia to the time the patient left the table.

The patient was placed in an oxygen tent after operation and kept there for four days. The convalescence was uneventful except for a period of 24 hours starting the day after operation. During this period the patient had a severe chill, a fever of 103.8° F. and symptoms which led us to diagnose a massive pulmonary atelectasis. However, following bronchial aspiration and intravenous fluids and blood the patient rallied, and on the third post-operative day her temperature became normal. Thereafter during the remainder of her stay in the hospital the temperature never exceeded 99.8° F. rectally or 99° F. by mouth. She was sitting up in bed by the end of the first week and out of bed a few days later. Her entire disposition changed; she became a happy, euphoric patient who was the favorite of the ward. A blood culture taken 24 hours after operation was negative, as were repeated cultures taken at intervals during the three weeks after operation that she remained in the hospital.

Her blood count showed an increase in hemoglobin and red cells. The white blood count remained about the same. The systolic blood pressure remained about 120 mm. Hg, but the diastolic rose to 80 mm. During the short period of reaction after operation the electrocardiographic tracing was indicative of paroxysmal auricular tachycardia, but 10 days later was "within normal limits."

Auscultation immediately after suture of the wound showed that the loud "machinery" murmur had completely disappeared. The heart sounds remained normal in every way, and these auscultatory findings were confirmed by the cardiac sound tracing.

Thirteen weeks after operation the girl was apparently a normal healthy individual whose tolerance for exercise had increased over what it had been before her attack of endarteritis.

*Note:* At present, two years after the operation, the girl is well, healthy and to all appearances living a normal life.

#### BIBLIOGRAPHY

1. GROSS, R. E., and HUBBARD, J. P.: Surgical ligation of a patent ductus arteriosus, Jr. Am. Med. Assoc., 1939, cxii, 729.
2. TOUROFF, A. S. W., and VESELL, H.: Subacute streptococcus endarteritis complicating patent ductus arteriosus. Recovery following surgical treatment, Jr. Am. Med. Assoc., 1940, cxv, 1270.
- TOUROFF, A. S. W.: A modified technique of surgical ligation of patent ductus arteriosus, Surgery, 1942, xii, 24.

---

#### TRICHINOSIS: A SPORADIC OUTBREAK WITH REPORT OF A CASE \*

By JAMES S. SWEENEY, Col., MC, F.A.C.P., FRANK B. QUEEN, Lt. Col., MC, and THOMAS F. BARRETT, Capt., MC, *Brigham City, Utah*

TRICHINOSIS is a disease about which little is written at the present time, partly because it is infrequently diagnosed. We are inclined, as are others, to suspect that chronic trichinosis is much more prevalent in this country than might be indicated by the literature and statistics.

The purpose of this paper is to draw attention to this condition and to report a case observed in this hospital. The patient was one of many victims of a very severe outbreak which led to an unusually interesting epidemiologic study.

#### CASE REPORT

Our patient, aged 32, was inducted into the Army September 5, 1942, at Butte, Montana. He never completed his basic training. He was assigned to the Medical Detachment at Bushnell General Hospital on September 25, 1942. He reported to sick call and was hospitalized in November 1942. His complaints were those of soreness in his back and legs for the preceding year and a half. He stated that these symptoms had grown progressively worse. Before induction into the Service he worked on a small farm. His mother was living at the age of 60 but was not well, being troubled with high blood pressure. His father had died in 1940 at the age of 63 of diabetes.

\* Received for publication November 13, 1943.  
Bushnell General Hospital.

mellitus complicated by gangrene. He had nine brothers living, three of whom he stated, had complaints similar to his. He had seven sisters living, five of whom likewise had similar complaints. One brother had died on December 26, 1937, from meningitis (actually trichinosis.)

The past history of our patient was essentially negative except for an attack of influenza in 1919, typhoid fever at the age of 15, and an attack of severe diarrhea in 1937. His physical examination was likewise essentially negative. He was a well developed and healthy appearing individual. There was a definite spasticity of the left gastrochemius muscle associated with tenderness in the proximal area of this muscle. There was subjective soreness in the right leg but no gross tenderness was elicited.

The patient's present illness began in the latter part of 1937. He stated that at this time, besides himself, others of his family and many friends became ill with similar symptoms. His illness followed the consumption of some home-cured sausage and ham, his symptoms appearing approximately 10 days after eating the hog meat. His trouble began with diarrhea, abdominal cramps, weakness and intermittent fever. About 10 days after the onset of these symptoms his eyes became swollen and, as he expressed it, he thought they were going to burst. There was an associated edema of his face. Three days later he developed severe pains all over his body, marked about his joints. These severe pains were intermittent in character and lasted for a period of approximately six weeks. There was some slight swelling of some of the joints at intervals. He also had considerable pain in his muscles of mastication and at times could hardly open his mouth. For a while he had to be fed with a tube. Throughout his acute illness there was profuse sweating.

The other members of the family had similar symptoms varying in degree and intensity. In addition to the symptoms the patient described, he stated that some of his brothers complained of severe itching and shortness of breath during the acute phase of their illness. Our patient was hospitalized during his illness for a period of 40 days and was discharged only to have a relapse and be readmitted, remaining the second time for a period of five weeks. Since his last discharge, he had felt only fairly well and his work had been limited to light farming. He stated that when he stood on his feet over a long period of time, the calves of his legs and back ached severely.

At the time the patient was observed in this hospital, all of the laboratory findings were essentially negative including the blood count, in which there was no increase of eosinophiles. Skin tests for trichinosis were also negative. Roentgenographic plates of his legs were negative. Because of the excellent history presented by this patient, it was felt that in all probability he had a trichinal infestation. A piece of muscle was, therefore, removed from his left leg for biopsy. Sections of the muscle studied at the National Museum revealed the larvae of trichina ranging from 570 to 640 cysts in 0.28 gm. of muscle. There was a total of 41 such cysts showing calcification and degeneration (these did not show in the roentgenograms).

As a result of these findings inquiry was made as to the other individuals afflicted from the same exposure experienced by our patient. We found through the Montana Health Department and other sources that in the Fall of 1937, our patient's family moved from North Dakota to Columbia Falls, Montana. They carried with them 12 of their pigs, and on their journey picked up 11 more in Eastern Montana. About the middle of October 1937, they began to kill their hogs for the purpose of securing their meat for the winter. They cured some of the hams and also made sausage. According to information obtained from Dr. H. F. Wilkins, Chief Deputy State Veterinarian of Montana, the products from the first three hogs killed between October 15 and November 10 were rather promptly consumed by the patient's family. These products were fried, roasted and boiled and there is some doubt as to whether

these hogs were infested with trichina, as they were fed separately from the others. On November 16 six more hogs were butchered, among which was a large stag. It is definitely known that the stag was heavily infested and that his meat constituted a large portion of that used in making smoked sausage. The sausage was put up in casings, smoked one day, rested one day, and then smoked three days, after which the family began eating it.

A party was held at the patient's home on December 14 and since no other hogs were killed until December 29, it seems that the six hogs just referred to above were the main offenders as far as the infested products were concerned.

It is reasonable to assume that the members of the household acquired their infestations some time following November 20 and during the early part of December, prior to the party of December 14. Details of sausage consumption by the family during this interim are not available. It is known, however, that the infested meat was eaten intermittently following its preparation which was completed on or about November 19 or 20. The exact incubation period, therefore, is difficult to establish in individual cases.

In one instance, namely, that of the 11 year old brother of our patient, there is some tangible evidence as to the incubation period. We are informed that on November 29 this youngster ate a large quantity of the smoked sausage. On December 2, he presented symptoms of excruciating abdominal pain, profuse vomiting, diarrhea and sweating. It is highly probable that this lad, as well as some of the rest of the family, had eaten some of the sausage prior to November 29, since the meat was ready for consumption on or about November 19 or 20. If this be true and our evidence is very strong that it is, it may be stated that the incubation period varied from three days to two weeks. Following the party on December 14, in a number of cases symptoms first appeared three, four, and five days later, up to and including two weeks, among those who were exposed at this time.

The laboratory findings in these cases are of interest, although they are incomplete. Of the 38 cases, there are records of eosinophile counts in 28. The percentage of eosinophiles varied from 0 to 70 per cent. The highest count of 70 per cent was that of the younger brother of our patient, who died from his infestation. The average of the eosinophile counts of those checked was 21 per cent. There were 23 skin tests done on the 38 patients of which 17 were positive and six were doubtful.

It is of interest to review in a little more detail some of the symptoms of the group infested and describe especially the course of the illness in the younger brother which terminated fatally. The symptoms in the order of their appearance were vomiting, diarrhea (5 to 20 pea soup stools per day without blood), griping abdominal pains, headache, severe pains across the back, puffiness about the eyelids and face, varying degree of photophobia, extreme soreness in the muscles of the arms and legs, and marked prostration with sweating in about 30 per cent of the cases. Approximately 15 per cent of the victims complained of intense itching. The temperature varied up to as high as 105° F.

The one fatal case was the 11 year old brother of our patient, just referred to above. He ate an unusually large quantity of home-cured sausage on November 29 and his symptoms began on December 2. There was a diminution of the intensity of his symptoms in a few days and the boy continued to eat the sausage when he felt like eating. On December 16, his condition grew worse and he was taken to the hospital with a recurrence of all the manifestations mentioned above in an exaggerated form. In addition he showed signs of meningeal irritation. A spinal puncture was done and live trichinae were found in the spinal fluid. After a very stormy course, the boy died on December 26, 10 days after his admission to the hospital.

There were several who were present in the gathering who did not eat any of

TABLE I

Case No.	Sex	Age	Date of Onset
1	M	15	November 22, 1937
2	M	27	November 24, 1937
3	M	30	November 28, 1937
4	M	21	November 28, 1937
5	M	11	December 3, 1937
6	M	32	December 3, 1937
7	F	16	December 5, 1937
8	M	13	December 5, 1937
9	F	29	December 5, 1937
10	M	3	December 5, 1937
11	M	31	December 6, 1937
12	F	19	December 7, 1937
13	M	29	December 7, 1937
14	F	9	December 7, 1937
15	F	41	December 8, 1937
16	F	55	December 9, 1937
17	M	25	December 9, 1937
18	M	20	December 9, 1937
19	M	44	December 12, 1937

## Guests at Party 14 December 1937

20	M	35	December 17, 1937
21	F	28	December 17, 1937
22	M	36	December 17, 1937
23	F	40	December 18, 1937
24	F	28	December 20, 1937
25	M	18	December 20, 1937
26	M	10	December 22, 1937
27	M	49	December 23, 1937
28	F	31	December 23, 1937
29	F	54	December 23, 1937
30	M	20	December 23, 1937
31	M	31	December 23, 1937
32	M	36	December 24, 1937
33	M		December 25, 1937
34	M	23	December 26, 1937
35	M	8	December 27, 1937
36	M	6	December 27, 1937
37	M	49	December 28, 1937
38	F	19	January 3, 1938

the hog meat and who, of course, showed no signs of illness. One family took some of the meat home with them but ate none of it at the party. Later they cooked it thoroughly and consumed it without any ill effects. In table 1 is a list of the cases, their age, sex, and date of onset of symptoms. These data have been provided by the Montana Health Department, local health service and the family physicians.

This interesting sporadic outbreak of trichinosis should be a warning to all the medical profession and health agencies. Those of us in the military hospitals should be on the alert for the recognition of trichinosis in cases of ill defined aches and pains and cases of unexplained eosinophilia. We are reminded, too, that frank symptoms of trichinosis may be present over a surprisingly long period of time—in our case for five years. It is not clearly understood just how long these parasites may remain viable in the human host. An investigation made on July 8, 1938, revealed that all the adults involved in this epidemic had residual symptoms of muscle soreness and at times acute muscle cramps in their legs. The residual symptoms were not so marked in children as in the adults. The adults were able to do some work, though they tired very easily and it was estimated that they were able to attend to from one quarter to one half of all their normal duties.

It is generally agreed that the severity of symptoms is proportional to the number of cysts ingested, as was so cogently demonstrated by the younger brother who continued to eat the infested sausage; also upon reinfestation because there is no immunity established as a result of one infestation. It should be remembered, finally, that other animals besides hogs may be carriers of the trichina, namely rats and bears. There is no known treatment for the state of encystment. The treatment during the acute phase or period of invasion is thorough catharsis supplemented with vermifuges. The most effective treatment is the prophylactic approach which involves simply thorough cooking of pork and sausages.

---

### DERMATITIS DUE TO BARBITURATES: REPORT OF A CASE WITH ASSOCIATED ANEMIA \*

By J. K. POTTER, M.D., and R. J. WHITACRE, M.D.,  
*East Cleveland, Ohio*

THE widespread use of barbiturates has resulted in numerous reports of reactions following their use. The type of reactions following ordinary doses of barbiturate is usually a form of dermatitis. Phenobarbital was introduced to the medical profession in 1911. A few months later Loewe<sup>1</sup> reported the first cutaneous reaction following the use of this drug. The skin manifestations were relatively mild and promptly disappeared upon withdrawal of the drug. Hamilton<sup>2</sup> reported the first case of universal exfoliative dermatitis due to phenobarbital in 1926. The majority of patients who have had skin reactions following the administration of barbiturates have recovered. However, fatal terminations have been reported.<sup>3, 4, 5, 6</sup>

\* Received for publication April 16, 1943.

The pathologic lesions associated with cutaneous reactions due to barbituric acid derivatives have not been clearly defined. Schulte<sup>7</sup> was unable to detect microscopic changes in the tissues of animals which had been subjected to repeated doses of barbiturates. Winer and Baer,<sup>8</sup> in reporting a fatal case of exfoliative dermatitis due to phenobarbital, stated that the autopsy findings were similar to those produced in toxic reactions to arsphenamine. There was a cellular infiltration of the internal organs by eosinophiles. Sexton, Pike, and Nielson<sup>9</sup> reported a case of exfoliative dermatitis and death due to phenobarbital. At autopsy there were no significant findings other than a bronchial pneumonia which was probably the result of drug depression. The following is a case report of dermatitis due to barbiturates associated with anemia.

#### CASE REPORT

On October 19 a white female, aged 46, in good physical condition, was admitted to the hospital for a thyroidectomy. The patient was receiving Lugol's solution, 15 minims three times a day, preoperatively. Temperature and respirations were normal, pulse 120, blood pressure 170 mm. Hg systolic and 98 mm. diastolic, basal metabolic rate + 28 per cent, hemoglobin 92 per cent, and red blood count 4,350,000. The white blood cell count was 7,500, with polymorphonuclears 76 per cent and lymphocytes 24 per cent. Repeated white blood cell counts during the patient's stay in the hospital did not reveal any material change. On October 20 luminal gr. 1½ (0.1 gm.) was given at 10:00 a.m. At 1:30 p.m. she had a chill followed by a rise in temperature which reached a maximum of 104° F. at 4:00 p.m. During this time a marked erythema developed over the entire body. On October 21 luminal gr. 1½ (0.1 gm.) was repeated at 12:00 m. Following this, the patient had a severe chill and by 4:00 p.m. the temperature was 103.8° F. At this time the erythema was even more pronounced and caused the patient considerable discomfort. Luminal and iodine medication was discontinued. Being unable to sleep the patient on October 22 at 1:30 a.m. was given amytal gr. 1½ (0.1 gm.) and aminopyrine gr. 3½ (0.23 gm.). This was followed promptly by a severe chill and the temperature was elevated to 103.6° F. by 2:30 a.m. At 8:00 a.m. the patient's temperature, pulse and respirations were normal, but her entire body was covered with large serous filled blebs. On this date the hemoglobin was reduced to 80 per cent and the red blood cells to 3,900,000. During the next few days the patient was very uncomfortable owing to the skin eruptions. The patient became progressively more anemic until October 29 when the hemoglobin was 58 per cent and the red blood count 3,000,000. At this time there were large indurated areas over the entire body and desquamation had started. Following this the general condition of the patient improved sufficiently for a thyroidectomy to be done. There were no further complications. Roth<sup>8</sup> has reported the occurrence of mild hyperchromic anemia in cases of exfoliative dermatitis due to barbiturates, but apparently anemia is an unusual complication.

The increased use of barbiturates as preoperative sedatives and as anesthetic agents makes it desirable to be aware of the relative frequency with which these reactions occur. Menninger,<sup>9</sup> in 1928, could find only 41 reported cases of cutaneous eruptions due to barbiturates. Since that time the number of cases reported in the literature has steadily increased. Many authors<sup>4, 9, 10, 11, 12, 13</sup> believe that from 1 to 3 per cent of patients taking phenobarbital will show a toxic skin rash. Cutaneous reactions apparently occur following all types of barbiturates. However, the long-acting barbiturates such as phenobarbital

(luminal) cause skin reactions more frequently than the short-acting barbiturates such as pentobarbital sodium (nembutal) or sodium propyl-methyl-carbinyl allyl barbiturate (seconal). Dietrich<sup>14</sup> has not observed cutaneous reactions in 3,700 cases in which seconal was used. In the last 10,000 recorded cases in which pentobarbital sodium was used we have not noted a single skin manifestation. The ultra short-acting barbiturates as pentothal sodium and evipal have been used extensively to produce surgical anesthesia but like the short-acting group they have rarely caused skin eruptions. This is significant to the surgeon and anesthetist because their use of barbituric acid derivatives is limited for the most part to the short-acting and ultra short-acting groups.

Various types of cutaneous reactions have been reported. The urticarial type in which wheals or angioneurotic edema occurs is the most common form. The onset occurs promptly and rapidly disappears upon discontinuing the drug. The erythematous type may become diffuse and go on to an exfoliative dermatitis. In other cases, vesicles, large blebs, or bullae occur which may become necrotic. Novy<sup>15</sup> described a fixed type of eruption which is characterized by recurrences of the skin manifestation in exactly the same location of the body. In these cases the involved area often becomes pigmented. Stryker<sup>16</sup> reported a case of erythematous dermatitis with red, swollen, exfoliative skin, stupor and rise of temperature due to a barbiturate which was followed by photo-sensitization of the skin. On exposure to sunlight four months later there was a reappearance of the dermatitis. Moss and Long<sup>17</sup> reported two cases that had in addition to the skin eruption involvement of all mucous surfaces except those of the bronchial and urinary system. No obvious loss of hair occurred, but each eventually shed all his finger nails and toenails. It has been noted<sup>4, 17</sup> that in certain cases an exudate may occur in the pharynx causing a pseudo-membrane suggesting diphtheria.

The dose of barbiturate is not an important factor, since very small quantities will produce skin eruptions in sensitive individuals.<sup>15</sup> Skin reactions may follow the administration of a single dose of barbiturate. However, it is believed<sup>18</sup> that these reactions occur more frequently after the repeated use of barbiturates, indicating that sensitization may be acquired. It has been suggested<sup>19</sup> that nearly all drug eruptions are in this category of acquired sensitization. At the present time there are no satisfactory tests to determine whether a patient is sensitive to barbiturates other than by clinical trial. The patch test and skin wheal are unreliable as methods of determining a patient's sensitivity.<sup>20, 15, 17</sup> It has been noted that patients who show intolerance to one barbiturate are often sensitive to other barbituric acid derivatives.

#### SUMMARY

A case of exfoliative dermatitis associated with anemia due to barbiturates is reported. Although barbiturates are very widely used it is not generally realized that certain groups of barbituric acid derivatives cause skin reactions in 1 to 3 per cent of the cases in which they are used. Occasionally these reactions terminate fatally. The skin eruptions usually occur with ordinary doses of the drug. In some instances repeated doses of a barbiturate increase the patient's sensitivity. In such cases dermatitis occurs after the continued use of the drug.



The long-acting barbiturates, such as phenobarbital, cause the greatest number of cutaneous reactions. The short-acting barbiturates, such as pentobarbital sodium, and the ultra short-acting barbiturates, such as pentothal sodium, rarely precipitate skin reactions.

## BIBLIOGRAPHY

1. LOEWE, S.: Klinische Erfahrungen mit Luminal, Deutsch. med. Wchnschr., 1912, xlii, 947.
2. HAMILTON, E. S., GEIGER, C. W., and ROTH, J. H.: Luminal poisoning with conjunctival residue, Illinois Med. Jr., 1926, xlix, 344.
3. CHAVANY, J. A., and VANNIER, P. E.: Toxidermic barbiturique à type d'érythème scarlatiniforme infiltré, Progrès Méd., 1929, xliv, 1685.
4. WILE, U. J., and BENSON, J. A.: Exfoliative dermatitis due to phenobarbital with fatal outcome: report of 2 cases, Ann. Int. Med., 1940, xiii, 1243.
5. SEXTON, D. L., PIKE, G. M., and NIELSON, A.: Exfoliative dermatitis and death due to phenobarbital, Jr. Am. Med. Assoc., 1941, cxvi, 700.
6. WINER, N. J., and BAER, R. L.: Exfoliative dermatitis due to phenobarbital, Arch. Dermat. and Syph., 1941, xliii, 473.
7. SCHULTE, T. L.: Tissue changes in chronic intoxication of barbital, California and West. Med., 1939, 1, 256.
8. ROTH, G. B.: The barbiturates and some of their side-effects, Med. Ann. Dist. Columbia, 1942, xi, 254.
9. MENNINGER, W. C.: Skin eruptions with phenobarbital (luminal), Jr. Am. Med. Assoc., 1928, xci, 14.
10. SCARLETT, E. P., and MACNAB, D. S.: Poisoning from phenobarbital (luminal), Canad. Med. Assoc. Jr., 1935, xxxiii, 635.
11. POOLE, A. K.: Drug reactions from barbital (veronal) and phenobarbital (luminal), Yale Jr. Biol. and Med., 1929, i, 345.
12. HUDDLESTON, J. H.: Non-dermatological disturbances during continued treatment with phenobarbital, Jr. Am. Med. Assoc., 1929, xciii, 1637.
13. TAYLOR, H. W., and SCHRAM, M.: Phenobarbital poisoning, Arch. Pediat., 1936, liii, 670.
14. DIETRICH, HARRY F.: Sodium propyl-methyl-carbinyl allyl barbiturate (seconal) as a sedative for infants and children: A clinical evaluation of one of the newer barbiturates, Anes. and Analg., 1943, xxii, 28.
15. NOVY, F. G.: Drug eruptions due to the barbiturates, California and West. Med., 1938, xlviii, 324.
16. STRYKER, G. V.: Barbituric acid dermatitis with photosensitization, Jr. Med., 1940, xx, 516.
17. MOSS, R. E., and LONG, W. E.: Toxic eruptions due to phenobarbital: report of two cases, Arch. Dermat. and Syph., 1942, xlv, 386.
18. BETHEA, O. W.: The barbituric acid salts, Internat. Med. Digest, 1932, xxi, 371.
19. WISE, F., and SULZBERGER, M.: Drug eruptions: I. Fixed phenolphthalein eruptions, Arch. Dermat. and Syph., 1933, xxvii, 549.
20. HILL, B. P.: Hypersusceptibility to basal anesthetics, Brit. Med. Jr., 1938, ii, 1199.

## SICKLE CELL ANEMIA SIMULATING CORONARY OCCLUSION\*

By S. L. ZIMMERMAN, M.D., Major, M.C., A.U.S., and ROY BARNETT, M.D.,  
Major, M.C., A.U.S., *Columbia, South Carolina*

## INTRODUCTION

REAL and fancied cardiac disease in sickle cell anemia has been the subject of considerable discussion.<sup>1, 2, 3, 4</sup> Particularly has there been confusion with rheumatic fever, as dyspnea, palpitation, cardiac enlargement, systolic and diastolic apical murmurs, and prolonged P-R intervals are associated with arthralgias and fever in both diseases. Klinefelter<sup>5</sup> has recently dispelled the confusion. He found cardiac hypertrophy without valvular or endocardial abnormalities, or myocardial damage in all 11 of his autopsied cases of sickle cell anemia. This may be compared with entirely similar findings in 22 of 23 cases of pernicious anemia reported by Cabot.<sup>6</sup> In both anemias the hypertrophy is secondary to the anemia, although the exact mechanism is still uncertain.<sup>7</sup> The clinical symptoms and signs reflect the hypertrophy and dilatation.

Severe anemias of any type may become manifest as functional coronary insufficiency, although there is some doubt whether this can occur in an otherwise normal heart.<sup>8</sup> A preëxisting coronary sclerosis is usually necessary to produce symptoms or electrocardiographic changes.<sup>8, 9</sup>

In our case the hemolytic crisis of sickle cell anemia was accompanied by typical clinical features and suggestive electrocardiographic changes of coronary occlusion.

## CASE REPORT

Patient L. J., a 30 year old colored male, was apparently well until June 1941, at which time, while carrying a bucket of coal, he was taken with a severe sense of substernal pain which radiated to both arms and was accompanied by profuse perspiration, nausea, and vomiting. He was hospitalized in the military service from June 10 to July 31, 1941. He denied syphilis, rheumatic fever, or other relevant illnesses. The family history was noncontributory.

On admission the temperature was subnormal, the blood pressure 110 mm. Hg systolic and 80 mm. diastolic. The heart was slightly enlarged to the left, and there was a soft blowing apical systolic murmur present. A tentative diagnosis of coronary occlusion was made. Admission electrocardiogram (A) on June 10, 1941, revealed an inverted T-wave in Lead IV-F and broad and low T-waves in Leads I and II. There were no significant ST deviations, although the tracing was not entirely satisfactory.

He soon became febrile and icteric. Blood count on June 13, 1941 revealed red blood cells 2.8 million, white blood cells 11,800, polymorphonuclears 89 per cent, and lymphocytes 11 per cent. On the smear there was marked achromia, anisocytosis,

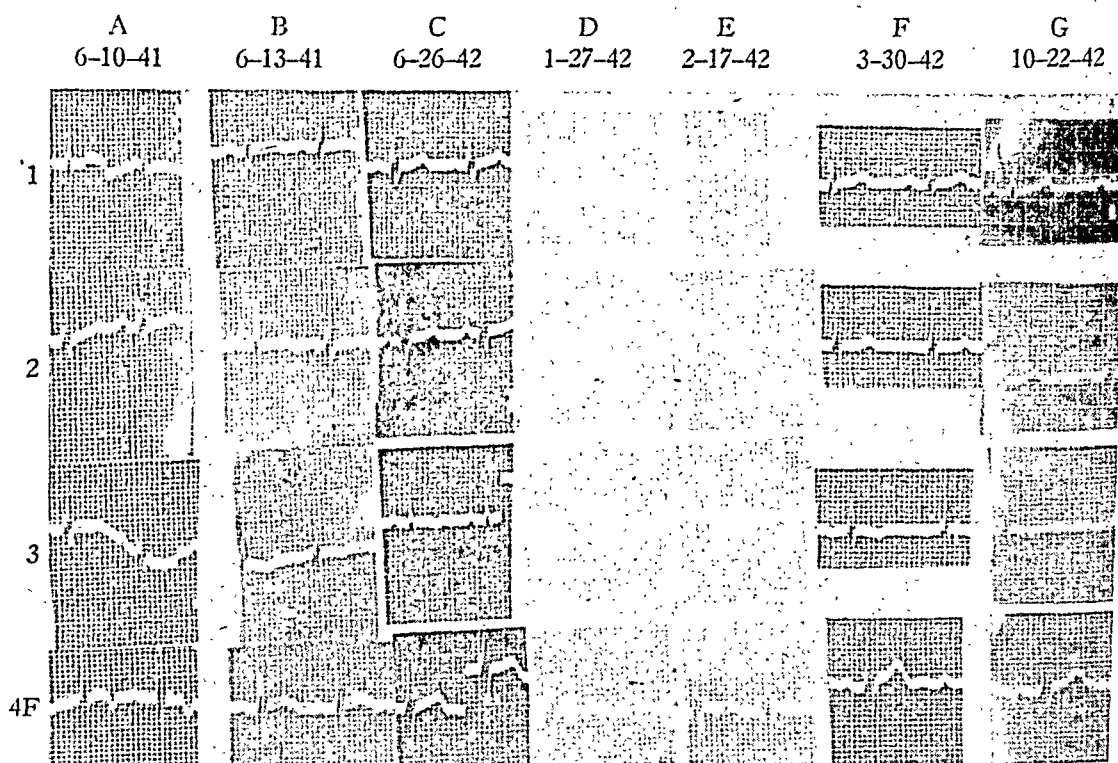
\* Received for publication May 3, 1943.

From Cardiovascular Service, U. S. Veterans Administration, Columbia, South Carolina.

Published with the permission of the Medical Director of the Veterans Administration who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

and poikilocytosis. Many sickle cells were reported. The Kahn reaction was negative. The urine was not remarkable. The icteric index was 36. On June 19, 1941 the red blood cells numbered 2.0 million. Many sickled forms were noted. The patient was placed on intramuscular liver extract, treated symptomatically and discharged July 31, 1941, improved, although available laboratory data recorded a final red blood cell count of 2.62 million with 50 per cent hemoglobin.

On the second electrocardiogram (B) taken three days after admission, the T-wave in IV-F was M-shaped and the T-wave in Lead II diphasic, but no ST deviations were apparent. There was moderate slurring of QRS in all leads. The third electrocardiogram (C) taken June 26, 1941, revealed a normally upright T-4 and increase in amplitude of the upright T-wave in Leads I and II. There was a



tendency toward right axis shift. At this time there was no longer any clinical evidence of a hemolytic crisis and the patient was asymptomatic.

The electrocardiographic changes described above were atypical in that they followed no particular pattern; however, they were not unlike those occasionally seen in anterior wall occlusions. They differed in that they occurred early and were unaccompanied by abnormal Q-waves or ST deviations. They reverted in a relatively short period of time.

The patient was readmitted November 7, 1941, for treatment of an acute non-suppurative lymphadenitis. At that time there was no evidence of an acute hemolytic crisis, although a marked anemia and sickling were present. The red blood cells averaged 2.5 million and the hemoglobin ranged between 50 and 70 per cent, by the Talquist method.

On January 27, 1942, he was readmitted, acutely ill, again complaining of severe chest pain, headache, nausea, vomiting, and prostration. He had been relatively well in the interim. The heart was large, the area of precordial dullness

extending to the anterior axillary line. There was a blowing systolic apical murmur. There was no evidence of congestive failure. The blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. The temperature reached a level of 102° F., but soon subsided. The pain persisted for a day or so and then subsided also. Blood studies again revealed the patient to be in an acute hemolytic crisis. There were electrocardiographic changes similar to those described above, namely, a small, broad T-1 and a notching of T-4 (IV-F). The final blood count of March 16, 1942, revealed a red blood cell count of 3.53 million with 70 per cent hemoglobin. The patient was subsequently transferred to a general hospital for disposition. Electrocardiogram F was taken while in remission, at which time his red blood cell count was 3.84 million and hemoglobin 75 per cent. Sickling remained present on all preparations, and the patient was discharged from the military service on March 21, 1942.

He was admitted to the Veterans Administration Facility, Columbia, South Carolina, October 22, 1942, at which time he was relatively asymptomatic. He was seen by the cardiologist, and the examination is quoted in full:

"Examination reveals a 30 year old colored male who is ambulant, minimally dyspneic at rest, with no distention of the cervical veins in the erect position. In the recumbent position it is seen that the cervical veins distend and pulsate very slightly but this is probably a transmitted pulsation. Trachea is midline, there is no tug. Thyroid is not enlarged. Apical impulse is rather forceful. The point of maximum intensity is felt in the fifth intercostal space outside the midclavicular line. The left border agrees to percussion. There is no demonstrable clinical enlargement to the right to percussion and there is no increase in retromanubrial dullness. Rhythm is regular. The first sound over the mitral area is not snapping, and is followed by a blowing apical systolic murmur. In the recumbent position and left lateral prone position, there is no essential change heard in the murmur described above. There is heard over the pulmonic area a systolic murmur as well."

The exercise tolerance was within normal limits. There was no evidence of congestive failure. The radial vessels were thickened, but there was no evidence of retinal sclerosis. Roentgenographic examination of the chest revealed cardiac en-

#### Laboratory Data for Admission October 22, 1942

October 22, 1942	Icterus index 20.
October 22, 1942	Wassermann: Positive 100 per cent. Kahn: 4-plus.
October 23, 1942	Urinalysis: Yellow, acid, sp. gr. 1.008. Mucus, occasional shred, 3-4 per high power field. Epithelia, few squamous and round, remainder negative.
October 22, 1942	Urinalysis: Amber, acid, sp. gr. 1.015. Mucus, few shreds. W.B.C., occasional. Epithelia, few squamous. Remainder negative.
October 22, 1942	Blood cell: Erythrocytes, 2,120,000. Hemoglobin, 7.1 grams, 45 per cent, Newcomer. Cell volume 46 per cent. Volume index 1.09. Red cells show definite sickling.
October 27, 1942	Blood count: Erythrocytes, 2,120,000. Leukocytes, 8,900. Blood platelets, 311,640. Differential leukocyte: polys, 46-43 seg, 3 staff. Lymphocytes, 54. Monos, none. Eosinophiles, none. Basophiles, none. Hemoglobin 7.3 grams, 45.2 per cent, Newcomer. Color index 1.07. Polychromatophilia present. Anisocytosis present. Poikilocytosis present. No myelocytes found. Reticulocytes, 9.2 per cent. Nucleated reds, none seen. Red cells show definite sickling.
November 5, 1942	Sedimentation index, 2 mm. per hour.
November 6, 1942	Gastric analysis: Amount obtained, 60 c.c. Total acidity, 50. Free HCl, 35.
November 12, 1942	Total erythrocyte count, 2,920,000. Leukocytes, 15,600. Polys, 52. Lymphocytes, 48. Hemoglobin, 9.0 grams, 56.7 per cent.

largement, the measurements being: M. R., 5.3 cm.; M. L., 11.3 cm.; Chest 30.6 cm. Fluoroscopy in the lateral and right oblique position revealed a uniform enlargement of the heart, but no evidence of unusual left auricular predominance was noted. There was no encroachment upon the esophagus. Roentgenographic examination of the skull revealed serrations in the vertex of the calvarium.

The patient remained afebrile, but laboratory work-up revealed a moderate to marked anemia with evidence of blood destruction and regeneration. The icteric index was elevated. Sickling was persistently present. The detailed laboratory data are given below. Interestingly enough the Wassermann and Kahn reactions became positive. Electrocardiogram G was within normal limits. With antisyphilitic therapy, iron and liver, and a high caloric diet, he was discharged with a final red blood cell count of 3.05 million and a hemoglobin of 7.6 grams, 47 per cent, New-comer method.

A final diagnosis of heart disease, due to sickle cell anemia with cardiac enlargement and myocardial damage, was made.

### DISCUSSION

Though minor electrocardiographic abnormalities, consisting of PR prolongation and variations in the amplitude of the T-wave, have been noted previously,<sup>5,10</sup> we have not discovered T-wave reversal or changes of this magnitude in other reported cases. In the present instance the progressive reversible T-wave changes increased the original suspicion of coronary-occlusion based on the clinical symptomatology.

There seems ample evidence that this is an instance of acute coronary insufficiency. It is very doubtful that any organic coronary artery disease exists, in view of the patient's age (30), race (negro), and the early return of the electrocardiogram to normal. Furthermore, the anemia per se could not have been the cause of the episodes described, as there was no change in red cell count during the recovery period. The necessary factor in the production of the coronary insufficiency was the hemolytic crisis. It is not possible to ascertain the exact mechanism, whether a sudden fall in red blood cells causing a sudden anoxemia, later compensated, or a toxic end product of red cell autolysis, or the same factor which induces the crisis itself.

### CONCLUSION

A case of sickle cell anemia is reported in which the hemolytic crisis simulated a coronary occlusion clinically and to a lesser degree cardiographically.

### BIBLIOGRAPHY

1. ANDERSON, W. W., and WARE, R. L.: Sickle cell anemia, *Am. Jr. Dis. Child.*, 1932, xliv, 1055.
2. ANDERSON, W. W., and WARE, R. L.: Sickle cell anemia, *Jr. Am. Med. Assoc.*, 1932, xcix, 902.
3. GRAHAM, G. S.: A case of sickle cell anemia with necropsy, *Arch. Int. Med.*, 1924, xxxiv, 778.
4. SYDENSTRIKER, V. P., MULHERIN, W. A., and HOUSEAL, R. W.: Sickle cell anemia; report of two cases in children, with necropsy in one case, *Am. Jr. Dis. Child.*, 1923, xxvi, 132.
5. KLINEFELTER, HARRY F.: The heart in sickle cell anemia, *Am. Jr. Med. Sci.*, 1942, cciii, 34.

6. CABOT, H. C.: Facts on the heart, 1926, W. B. Saunders, Philadelphia and London.
7. FISHBERG, ARTHUR M.: Heart failure, 1940, Lea and Febiger, Philadelphia.
8. KATZ, LOUIS N.: Clinical aspects of the electrocardiogram, 1941, Paul B. Hoeber, Inc., New York.
9. PARDEE, HAROLD E. B.: Electrocardiography, 1941, Lea and Febiger, Philadelphia.
10. KING, J. T., and JANEWAY, C. W.: Sick cell anemia with cardiac complications, Internat. Clin., 1937, iii, 41.
11. PORTER, W. B.: Heart changes and physiologic adjustment in hookworm anemia, Am. Heart Jr., 1937, xiii, 550.

## EDITORIAL

### *CUSHING'S SYNDROME*

SINCE Cushing's original description<sup>1</sup> of this symptom complex, the condition has become widely known, doubtless because of the striking and unusual symptoms it presents, in spite of its relative rarity. Cushing attributed the syndrome to a basophilic adenoma of the anterior lobe of the pituitary because this lesion was found in several of the 12 cases he collected. Following his report the syndrome was widely regarded as a manifestation of hyperpituitarism.

Subsequent observations, however, have cast serious doubt on this conclusion. There is no constant relationship between the occurrence of basophilic adenomata and the symptom complex. Many patients with basophilic adenomata have been reported who did not show these symptoms. Conversely, many clinically typical cases of the syndrome have shown no pituitary adenoma, but often a tumor or other significant lesion elsewhere, most frequently in the adrenal cortex, or more rarely in the thymus.

Moreover, a critical survey of the principal symptoms reveals that many of them suggest a deficiency rather than an overactivity of the pituitary. Among the most prominent features may be mentioned the obesity, often painful, commonly described as the "buffalo" type, affecting especially the face, neck, the trunk and markedly the abdomen, and sparing the limbs. Cutaneous changes are marked and include hypertrichosis, dryness and fragility of the skin with marked acne and susceptibility to superficial infections, a dusky flushing which may be associated with an actual polycythemia, and the characteristic purplish atrophic striae on the abdomen and thighs. Occasionally there may be a cutis marmorata, ecchymoses, or brownish pigmentation.

There is usually hypertension and more or less marked generalized arteriosclerosis. There is progressive weakness and prostration, with pains in the back, limbs and abdomen.

There is usually a kyphosis of the dorsal spine, accentuating the buffalo appearance. There is also in most cases a general reduction in the density of the bones, an osteoporosis which may become extreme and lead to pathological fractures, including compression fractures of the vertebral bodies. The pathogenesis of this change is still in doubt, but there is no convincing evidence that it is due to hyperparathyroidism.

Eventually there is usually evidence of depressed thyroid activity, as shown by a reduced basal metabolic rate and a high blood cholesterol. Gonadal activity is also depressed as indicated by amenorrhea, loss of libido and arrest of normal development of ovarian follicles in females and cor-

<sup>1</sup> CUSHING, HARVEY: *Papers relating to the pituitary body, hypothalamus and parasympathetic nervous system*, 1932, Charles C. Thomas, Springfield, Ill.

responding disturbances in males. Less constantly but frequently there is a disturbance of carbohydrate metabolism with hyperglycemia and glycosuria. There may also be a disturbance of water balance with polyuria and polydipsia.

These varied symptoms indicate a marked and wide spread endocrine disturbance and suggest a general depression of function (except for the adrenal cortex) which may in considerable measure be a direct or indirect result of a deficiency of hypophyseal secretion. The adrenal cortex, on the other hand, appears in many cases to be hyperactive. In a substantial portion of the cases of Cushing's syndrome there have been found either cortical tumors or a well marked diffuse hyperplasia of the cortex. Removal of such a tumor has been followed by a remission of symptoms.<sup>2</sup> However, such adrenal lesions have been demonstrated in only a portion of the cases, and no single gross lesion has been found constantly present in all cases.

In 1935 Crooke<sup>3</sup> reported a study of 12 cases of Cushing's syndrome in all of which he found a hyalinization of the cytoplasm of the basophilic cells of the hypophysis which he interpreted not as a degenerative or necrobiotic change but as an indication of a physiological disturbance which he thought might furnish a basis for the development of Cushing's syndrome. Of these 12 cases, 6 showed a basophilic adenoma of the pituitary, three a tumor of the adrenal cortex, and three a tumor of the thymus. This hyalinization was not present in appreciable degree in a large number of control cases, including cases of acidophilic and basophilic cell adenomata of the pituitary which did not show the Cushing syndrome clinically. Crooke's observations as to the hyaline change in the basophilic cells in Cushing's syndrome have been confirmed by Rasmussen<sup>4</sup> in three cases and by Heinbecker<sup>5</sup> in five cases. The exact significance of this hyalinization is not yet clear, however, nor has any single cause for its development been found.

As accumulating evidence tended to discredit the significance of basophilic adenomata as a cause of Cushing's syndrome, interest has centered increasingly on the adrenal cortex. As has been noted, cortical tumors and diffuse hyperplasia of the adrenal cortex constitute the most frequent potentially significant lesions found in these cases. Among others, Albright and his associates<sup>6</sup> have supported the view that the syndrome is the result of "hyperadrenocorticism." It has not been possible clinically to differentiate

<sup>2</sup> RAYD, JACOB M.: Cortical carcinoma of the adrenal with adrenogenital syndrome associated with an adenoma of the pituitary, *Am. Jr. Path.*, 1935, xviii, 764.

<sup>3</sup> CROOKE, A. C.: Change in basophile cells of pituitary gland common to conditions which exhibit syndrome attributed to basophile adenoma, *Jr. Path. and Bact.*, 1935, xli, 339-349.

<sup>4</sup> RASMUSSEN, A. T.: Relation of basophilic cells of human hypophysis to blood pressure, *Endocrinology*, 1936, xx, 673-678.

<sup>5</sup> HEINBECKER, P.: The pathogenesis of Cushing's syndrome, *Medicine*, 1944, xxiii, 225-247.

<sup>6</sup> ALBRIGHT, F., PARSON, W., and BLOOMBERG, E.: Cushing's syndrome interpreted as hyperadrenocorticism leading to hypergluconeogenesis; results of treatment with testosterone propionate, *Jr. Clin. Endocrinol.*, 1941, i, 375-384.



cases with adrenal cortical lesions from cases without them with any certainty.

Recent observations of Heinbecker<sup>5</sup> appear to throw light on some of the cases of Cushing's syndrome which do not have adrenal lesions. By the experimental production of destructive lesions in the hypothalamus he was able to produce in dogs a condition showing some of the features of Cushing's syndrome in man. The animals became obese and showed diabetes insipidus. They showed changes in the thyroid, gonads and (in some individual animals) in the pancreas which were interpreted as regressive and indicating depression of function. The adrenals were normal. There was a loss of granulations in the basophilic cells of the anterior lobe of the pituitary, although the hyalinization seen in human cases was not exactly duplicated. These animals were abnormally sensitive to the administration of adrenal cortical hormone.

He also made a careful study of this portion of the brain in five human cases of Cushing's syndrome. In one case which showed an adrenal tumor, no abnormalities were found in the hypothalamus. In all the other four cases which showed normal adrenals he found a marked degree of atrophy of the nerve cells in the hypothalamic nuclei. In two of the cases a small basophilic adenoma of the anterior pituitary was noted, but not in the others. All cases, however, showed the hyalinization of the basophilic cells described by Crooke. This Heinbecker also regards as the significant lesion common to all cases, and he believes it indicates a depression of function which results also in a secondary depression of the gonads and the thyroid. Basophilic adenomata, if present, he thinks are of secondary significance and suggests that they may indicate an attempt on the part of the anterior pituitary to compensate for decreased function of the basophilic cells. This hyalinization and depression of function of the basophilic cells may be due directly to pathological overactivity of the adrenal cortex or to a tumor of the thymus, or it may result from atrophy of the hypothalamic nuclei with an apparently normal adrenal function. Based on his animal experiments, Heinbecker suggests that the hypothalamic lesion may operate by increasing the sensitiveness of the hypophysis to cortical hormone, so that a normal cortical secretion may bring about the same changes in the basophilic cells that are caused by a hypersecretion in individuals with a normal hypothalamus.

There is not as yet sufficient evidence to decide these points, and a solution perhaps may wait until adequate methods are available for identifying and measuring the hormones presumably concerned. Meanwhile, in the present state of knowledge, the most promising therapeutic approach appears to be a search for a lesion in the adrenals (or thymus) rather than a direct attack on the pituitary, whether by surgical or roentgenological measures.

## REVIEWS

*Textbook of Gynecology.* Second Edition. By EMIL NOVAK, M.D., F.A.C.S. 708 pages; 16.5 × 24 cm. 1944. Williams and Wilkins Company, Baltimore. Price, \$8.00.

Although only three years have elapsed since the appearance of the first edition, this new volume of Dr. Novak's textbook is in many ways a new book.

The present treatment of the topic of generative embryology as a single chapter is a definite improvement. The collaboration of Dr. Meyers in this chapter makes the book of great value to specialists as well as students.

The addition of a chapter on female urology, by one of the outstanding men in this field, gives the student and general practitioner an insight into the close relationship between gynecological and urological conditions.

The text of the book continues to be a little lengthy and repetitious. The illustrations are more numerous but, as in the first edition, lack the simplicity which is so essential in presenting the problem of gynecology to students. However, both criticisms are minor ones, and in general the second edition deserves the same success as the first.

W. K. D.

*X-Ray Examination of the Stomach.* By FREDERIC E. TEMPLETON, M.D. 516 pages; 23.5 × 16 cm. 1944. University of Chicago Press, Chicago. Price, \$10.00.

With the exception of lipiodol myelography, fluoroscopy is more vital in making a roentgen diagnosis in diseases of the gastrointestinal tract than any other phase of roentgenology. In preparing his volume of roentgen-ray diagnosis of the upper gastrointestinal tract, Dr. Frederic E. Templeton evidently had this belief in mind, for he repeatedly emphasizes the fluoroscopic appearance of lesions of the upper gastrointestinal tract, and his differential diagnoses are based largely on the findings made while the patient is being examined fluoroscopically.

The material of the book is divided into a section dealing with the spot filming fluoroscope and the technic of using this machine, and other sections discussing the diseases of the esophagus, stomach and duodenum. Since few doctors have a spot filming fluoroscope available, this portion of the book is of only passing interest. The other sections, though, are well worth careful perusal, for the descriptions of roentgenological evidence of diseases of the esophagus, stomach and duodenum are clear, concise and accurate. Profuse illustrations have been inserted throughout the text, and the only comment needed concerning these is that they are adequate in number and are excellent.

Throughout the book, there are frequent references to the patterns of the mucosa of the esophagus, stomach and duodenum. There is no doubt left in the reader's mind that the author considers the mucosal patterns to be of paramount importance in locating and differentiating the lesions in question. Numerous pages are devoted to describing in detail the normal and the abnormal mucosal patterns as seen by the author and others. Perhaps the greatest criticism that can be made of this book is the innumerable references to the works of other roentgenologists and gastroenterologists who, as is so common among doctors, have contradictory views about the mucosa of the gastrointestinal tract. If one is particularly interested in research as regards the roentgenographic appearance of the mucosa, then the numerous references will be of help, but to the average physician, this part of the book will be only confusing and tiresome.

The author's last chapter is perhaps his most useful one to the reader. Here, in a brief though complete summary, the various points of differential diagnosis of lesions of the upper gastrointestinal tract are enumerated and compared. Thus, the busy practitioner can quickly consult this chapter, to aid him in his work, without having to read through one of the more lengthy ones. If this text is found to be inconclusive on some particular subject, or if further reading is desired, the author has a very long list of references added; this bibliography contains the names of not only American writers, but many foreign ones.

The reviewer has no hesitancy in stating that this volume of Dr. Templeton's is worthy of reading, for the information to be gained far outweighs the effort required to read it. The selling price of \$10 might be considered a little excessive for a book no larger than this one, but, like the references of the mucosal patterns, this is a debatable point.

D. J. B.

*Gynecological and Obstetrical Urology.* By HOUSTON S. EVERETT, A.B., A.M., M.D. 517 pages; 23.5 × 16 cm. 1944. Williams and Wilkins Company, Baltimore. Price, \$6.00.

This book represents the first correlation of the specialties of gynecology and obstetrics with that of urology. The importance of the interrelationship of each can not be too firmly stressed, and is something that becomes more obvious as the text of Dr. Everett's book is carefully reviewed.

The author has had wide experience in this work, at both the Johns Hopkins and Maryland University Medical Schools. He has also had personal association with the outstanding authorities in these fields. In addition he has the rare faculty of intelligent interpretation and logical organization.

The book is one which the specialist will find an indispensable working guide to his urological problems. It is also the type of volume which becomes of increasing value to the general practitioner in this daily contact with women.

The chapter on cystoscopy sets forth simply and clearly the technic for the Kelly method of aeroscopic cystoscopy, and omits for the most part the finer details of the more familiar water method. This should prove itself of value to all those who have heard of this method, but until now have been unable to put it into practice for lack of an authoritative description of the technic. However, in all fairness to the method, it must not be assumed to be so simple as to require neither training nor experience, for without these cystoscopy by the Kelly method will lead only to confusion. The Kelly method is for many procedures unexcelled, but in others it is inferior to the water method. Training and judgment are needed to select the proper method for any individual case.

Dr. Everett's treatment of the topic of bladder inflammations is excellent, and he has here brought up to date the complicated picture of chemotherapy. Other sections equally well written are those of calculi and renal tuberculosis, both at best difficult to present.

The illustrations are all of good-quality and clarity. The drawings by Malone, a student of the late Max Brodel, are entirely accurate and understandable. The views of the interior of the bladder made through the Kelly cystoscope may be confusing to those urologists accustomed only to the picture as seen through the water scope.

The criticisms of this review are made in a constructive sense, and in no way affect the opinion that Dr. Everett's book is to be the authority for urological problems in women.

W. K. D.

## BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Surgery of the Hand.* By STERLING BUNNELL, M.D. 734 pages; 26 × 19 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, \$12.00.

*Proteins and Amino Acids—Physiology, Pathology, Therapeutics.* 189 pages; 23 × 15 cm. 1944. The Arlington Chemical Company, Yonkers, New York.

*The Diseases of the Endocrine Glands.* By HERMANN ZONDEK, M.D. (Berlin). Fourth (Second English) Edition. Translated by CARL PRAUSNITZ GILES, M.D. (Breslau), M.R.C.S. (Eng.), L.R.C.P. (Lond.). 496 pages; 23.5 × 15.5 cm. 1944. Williams and Wilkins Company, Baltimore. Price, \$11.00.

*Ventures in Science of a Country Surgeon.* By ARTHUR E. HERTZLER, M.D. 304 pages; 23.5 × 16.5 cm. 1944.

*Gynecological and Obstetrical Urology.* By HOUSTON S. EVERETT, A.B., A.M., M.D. 517 pages; 23.5 × 16 cm. 1944. Williams and Wilkins Company, Baltimore. Price, \$6.00.

*The Medical Clinics of North America.* Boston Number. Twenty-two contributors. 263 pages; 23 × 15 cm. September, 1944. W. B. Saunders Company, Philadelphia. (Published bi-monthly—price per year, \$12.00.)

*Recent Advances in Anaesthesia and Analgesia (Including Oxygen Therapy).* Fifth Edition. By C. LANGTON HEWER, M.B., B.S. (Lond.), D.A. (Eng.). 343 pages; 21 × 14 cm. 1944. The Blakiston Company, Philadelphia. Price, \$5.50.

*Physiology in Health and Disease.* Fourth Edition, thoroughly revised. By CARL J. WIGGERS, M.D., D.Sc., F.A.C.P. 1174 pages; 24 × 16 cm. 1944. Lea & Febiger, Philadelphia. Price, \$10.00.

*Studies on Immunisation.* Second Series. With appendices dealing with anti-typhoid inoculation, chemo-therapy, and statistical and other operations of induction. By SIR ALMROTH E. WRIGHT, M.D., F.R.S. 256 pages; 25.5 × 19.5 cm. 1944. William Heinemann, Medical Books, Ltd., London. Price, 25s net.

*A Method of Anatomy—Descriptive and Deductive.* Third Edition. By J. C. BOILEAU GRANT, M.C., M.B., Ch.B., F.R.C.S. (Edin.). 822 pages; 26 × 18 cm. 1944. Williams and Wilkins Company, Baltimore. Price, \$6.00.

*Diagnóstico Topográfico de los Procesos Pleuropulmonares. Estudio Anatómico, Clínico y Radiológico.* By DR. JUAN SOTO BLANCO. (Colección de Monografías—Monografía No. 1.) 106 pages; 29 × 20.5 cm. 1944. Imprenta "Rosgal," de Hilario Rosillo, Montevideo, Uruguay.

*Primera Conferencia Argentina, Buenos Aires, October of 1943.* Relatos Oficiales, Contribuciones y Discusiones. 307 pages; 20 × 14 cm. 1943. Published under the direction of Dr. Santiago I. Nudelman, Secretary, Buenos Aires.

## COLLEGE NEWS NOTES

### ADDITIONAL A. C. P. MEMBERS ENTER THE ARMED FORCES

Dr. J. Roscoe Miller, F.A.C.P., Chicago, Dr. Gustavus A. Peters (Associate), Rochester, Minn., and Dr. Harry A. Senekjic (Associate), New Orleans, have recently entered the Armed Forces, bringing the total number of members on active military duty to 1,720.

Lt. Comdr. James P. Jordan (Associate), (MC), USNR, of Buffalo, N. Y., died July 23, 1944.

---

### NEW LIFE MEMBERS

The College is gratified to announce that the following Fellows of the College became Life Members during the month of November:

Dr. Thomas P. Murdock, Meriden, Conn.  
Dr. Delivan A. MacGregor, Wheeling, W. Va.  
Dr. Leon S. Gordon, Washington, D. C.

---

### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

#### *Reprints*

Dr. A. J. Atkinson (Associate), Chicago, Ill.—1 reprint.  
Dr. Benjamin M. Berstein, F.A.C.P., Brooklyn, N. Y.—2 reprints.  
Charles A. Bohnengel, F.A.C.P., Captain, (MC), AUS—1 reprint.  
Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn.—1 reprint.  
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—7 reprints.  
Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y.—3 reprints.  
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—3 reprints.  
Dr. William Nimeh, F.A.C.P., Mexico City, D. F.—1 reprint.  
Joseph F. Painton, F.A.C.P., Lieutenant Colonel, (MC), AUS—1 reprint.  
Michael Peters (Associate), Captain, (MC), AUS—1 reprint.  
Dr. William S. Reveno, F.A.C.P., Detroit, Mich.—1 reprint.  
Morgan Y. Swirsky (Associate), Lieutenant, (MC), AUS—1 reprint.  
Dr. Michael Weingarten (Associate), New York, N. Y.—1 reprint.  
Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.—8 reprints.

---

### DR. CHESTER S. KEEFER APPOINTED GOVERNOR FOR MASSACHUSETTS

Dr. Chester S. Keefer, F.A.C.P., Boston, was appointed, during November, by President Ernest E. Irons, the College Governor for the state of Massachusetts, to succeed the late Dr. William B. Breed. All local matters concerning the College, including proposals for membership, shall in the future be cleared through Dr. Keefer, whose address is 65 East Newton Street, Boston 18.

## NEW COMMITTEE APPOINTMENTS

Dr. George F. Strong, F.A.C.P., Vancouver, B.C., has been appointed a member of the Committee on Constitution and By-Laws, to succeed the late Dr. Charles H. Cocke. Dr. James E. Paullin, F.A.C.P., Atlanta, already a member of the Committee on Constitution and By-Laws, will serve as Chairman.

Dr. Roger I. Lee, F.A.C.P., Boston, has been appointed a member of the Committee on Educational Policy to succeed the late Dr. Charles H. Cocke.

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, has been appointed a member of the Committee on Post-War Planning for Medical Service to succeed the late Dr. William B. Breed.

## RESOLUTION FROM KENTUCKY STATE MEDICAL ASSOCIATION

The War-Time Graduate Medical Meetings Committee has coöperated during 1943 and 1944, in the program of the Kentucky State Medical Association, wherefor the following resolutions have been received:

"WHEREAS, The programs of the Kentucky State Medical Association for 1943 and 1944 have been most instructive and valuable as postgraduate courses for the rank and file of the profession, and

"WHEREAS, The success of these programs is wholly due to the splendid coöperation of the American Medical Association, the American College of Surgeons, the American College of Physicians, through the National War-Time Graduate Medical Meetings, and the essayists of national reputation whom they have furnished,

"THEREFORE, BE IT RESOLVED, That the House of Delegates, being duly assembled on this 94th Annual Meeting, go on record as expressing our appreciation to these national associations for their war-time contribution to our Association and the representatives of the Armed Forces in attendance, and

"BE IT FURTHER RESOLVED, That this Resolution be spread upon the Minutes of this Association, and in further testimony of our appreciation, that a copy of this Resolution be forwarded to the respective associations having participated in these programs."

## OPPORTUNITIES FOR INTERNS AND RESIDENTS IN PSYCHIATRY, ST. ELIZABETH'S HOSPITAL, WASHINGTON

The United States Civil Service Commission is accepting applications for War Service Appointments as medical officers (rotating internship and psychiatric resident) for St. Elizabeth's Hospital, Washington, D. C., at \$2,433.00 a year. St. Elizabeth's Hospital is an institution for the treatment of mental disorders. It has a 500-bed medical and surgical service. Full information and application forms can be obtained from the United States Civil Service Commission, Washington 25, D. C.

## AN EXPERIMENT BY THE NEW YORK ACADEMY OF MEDICINE—PERMANENT DRUG EXHIBIT

Thirty-eight of the leading pharmaceutical companies of the United States are collaborating with the New York Academy of Medicine Committee on Drug Exhibits, of which Dr. Walter A. Bastedo, F.A.C.P., is Chairman, in an exhibit of drugs and other pharmaceuticals currently employed in combating infectious diseases.

From time to time the Committee will replace the present exhibit with a new one illustrating the latest developments in the pharmaceutical world.

The State Medical Society of Wisconsin announces its 1945 annual meeting at Milwaukee, October 7-10.

---

#### AMERICAN UROLOGICAL ASSOCIATION OFFERS AWARD

The American Urological Association offers an annual award not to exceed \$500.00, for an essay (or essays) on the result of some specific clinical or laboratory research in urology. Competitors are limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. Essays should be submitted to the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1945.

---

#### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the Army, addressed the Fifth Congress of the Army Service Forces Training Agencies at Camp Barkeley, Texas, October 24-26. The purpose of the conference was to review the 1944 Army Service Forces training plan and to explain future plans.

#### General Lull Talks on Health of Army

Hospital admission records show there has been a striking decline in the incidence of many diseases in this war compared with the first World War, Major General George F. Lull, F.A.C.P., U. S. A., Deputy Surgeon General of the Army, told the International College of Surgeons which met at Philadelphia on October 3. The pneumonia rate, he said, has dropped from 19.0 to 12.8, the measles rate from 23.8 to 5.8, mumps from 55.8 to 6.2, scarlet fever from 2.8 to 1.6, meningococcic meningitis from 1.2 to 0.8, tuberculosis from 9.4 to 1.2 and venereal disease from 86.7 to 41.0. These figures represent annual hospital admission rates per thousand strength. Similarly the death rate from all diseases with the exception of deaths due to influenza epidemic dropped from 14.1 in World War I to 0.6. The Army's influenza rate, which was 5.97 in World War I, has become negligible, being represented statistically by 0.00 on this basis.

#### Recent Promotions, Medical Corps Officers

##### *Major to Lieutenant Colonel*

Samuel Morrison, F.A.C.P., Baltimore, Md.  
Oliver Joseph Menard, F.A.C.P., Long Meadow, Mass.  
Kendall Elsom, F.A.C.P., Philadelphia, Pa.

The Madigan General Hospital at Fort Lewis, Washington, was named in honor of the late Colonel Patrick Sarsfield Madigan, (MC), F.A.C.P., for his long and faithful service in the Army Medical Corps.

#### University of Maryland Honors General Kirk

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, recently received the honorary degree of Doctor of Science from his alma mater, the University of Maryland. The citation was read by Major General Robert U. Patterson, F.A.C.P., Dean of the Medical School and former Surgeon General of the Army. General Kirk addressed the graduates of the Schools of Medicine and Nursing and presented their diplomas. Prior to the ceremonies, Dr. Byrd, President

of the University of Maryland, and members of the faculty of the Medical School gave a dinner in honor of General Kirk at the Hotel Belvedere.

#### Colonel Baker Awarded Legion of Merit

Colonel Benjamin M. Baker, F.A.C.P., Baltimore, has been awarded the legion of merit by General Douglas B. MacArthur for "exceptionally meritorious conduct in the performance of outstanding services in the South Pacific Area from April 20, 1942, to June 13, 1944."

The National Committee for Mental Hygiene has elected Major General Norman T. Kirk, F.A.C.P., The Surgeon General, as one of its six new members in recognition of his "unusual awareness of the importance of skilled psychiatric treatment in the Army."

Dr. Carl V. Moore, F.A.C.P., Associate Professor of Medicine, Washington University, St. Louis, Mo., is a recent appointee to the Army Epidemiological Board.

#### Army Medical Consultants Convene at White Sulphur Springs

The Service Command Consultants in Medicine and civilian physicians who are Consultants in Medicine to The Surgeon General and the Secretary of War convened at White Sulphur Springs, Va., October 30-31. Among those in attendance were Major General Norman T. Kirk, F.A.C.P., The Surgeon General, Colonel W. Paul Holbrook, F.A.C.P., Chief of Professional Service, Army Air Forces, Colonel Arden Freer, F.A.C.P., Chief of Professional Administrative Service, Lieutenant Colonel Francis R. Dieuaide, F.A.C.P., Chief of Tropical Disease Treatment Branch, Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant in Medicine to The Surgeon General, Colonel Walter Bauer, F.A.C.P., Consultant in Medicine, Eighth Service Command, Colonel E. V. Allen, Consultant in Medicine, Seventh Service Command and Lieutenant Colonel Joseph A. Hayman, Jr., F.A.C.P., Chief of Medical Service, Moore General Hospital, Swannanoa, N. C.

Lieutenant Colonel Phillip T. Knies, F.A.C.P., of Columbus, Ohio, Army member of the Interdepartmental Quarantine Commission, has been assigned as Army Quarantine Liaison Officer to The Surgeon General of the Army and is stationed in the Epidemiology Division, Preventive Medicine Service.

#### Wakeman Field Sanitary Area Dedicated

A model sanitary demonstration area was dedicated in October at Carlisle Barracks, Pa. It has been named Wakeman Field in memory of the late Colonel Frank B. Wakeman, F.A.C.P., who was Director of the Training Division, Office of The Surgeon General and former Instructor in the Department of Military Sanitation at Carlisle Barracks. Guest speakers stressed the importance of rigid sanitary measures in the field to prevent the spread of disease.

#### Army Trains Clinical Psychologists

An officers course in clinical psychology was inaugurated in October at the Adjutant General's School, Fort Sam Houston, Tex. The welcoming address was given by Lieutenant Colonel James B. Polka, Chief of the neuropsychiatry section of Brooke General Hospital, Fort Sam Houston, Tex., who represented Brigadier General George C. Beach, Jr., F.A.C.P., the hospital's Commanding General. Lieutenant Colonel Morton G. Seidenfeld, AGD, Chief Clinical Psychologist and Liaison with the Office of The Surgeon General, spoke on the duties and responsibilities of the clinical psychologist.

Representing The Surgeon General, Lieutenant Colonel Malcolm J. Farrell, MC, Assistant Director of the Neuropsychiatry Consultants Division, spoke on the relationship between the psychologist and psychiatrist in Army hospitals.



The State Medical Society of Wisconsin announces its 1945 annual meeting at Milwaukee, October 7-10.

---

#### AMERICAN UROLOGICAL ASSOCIATION OFFERS AWARD

The American Urological Association offers an annual award not to exceed \$500.00, for an essay (or essays) on the result of some specific clinical or laboratory research in urology. Competitors are limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. Essays should be submitted to the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1945.

---

#### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the Army, addressed the Fifth Congress of the Army Service Forces Training Agencies at Camp Barkeley, Texas, October 24-26. The purpose of the conference was to review the 1944 Army Service Forces training plan and to explain future plans.

#### General Lull Talks on Health of Army

Hospital admission records show there has been a striking decline in the incidence of many diseases in this war compared with the first World War, Major General George F. Lull, F.A.C.P., U. S. A., Deputy Surgeon General of the Army, told the International College of Surgeons which met at Philadelphia on October 3. The pneumonia rate, he said, has dropped from 19.0 to 12.8, the measles rate from 23.8 to 5.8, mumps from 55.8 to 6.2, scarlet fever from 2.8 to 1.6, meningococcic meningitis from 1.2 to 0.8, tuberculosis from 9.4 to 1.2 and venereal disease from 86.7 to 41.0. These figures represent annual hospital admission rates per thousand strength. Similarly the death rate from all diseases with the exception of deaths due to influenza epidemic dropped from 14.1 in World War I to 0.6. The Army's influenza rate, which was 5.97 in World War I, has become negligible, being represented statistically by 0.00 on this basis.

#### Recent Promotions, Medical Corps Officers

##### *Major to Lieutenant Colonel*

Samuel Morrison, F.A.C.P., Baltimore, Md.  
Oliver Joseph Menard, F.A.C.P., Long Meadow, Mass.  
Kendall Elsom, F.A.C.P., Philadelphia, Pa.

The Madigan General Hospital at Fort Lewis, Washington, was named in honor of the late Colonel Patrick Sarsfield Madigan, (MC), F.A.C.P., for his long and faithful service in the Army Medical Corps.

#### University of Maryland Honors General Kirk

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, recently received the honorary degree of Doctor of Science from his alma mater, the University of Maryland. The citation was read by Major General Robert U. Patterson, F.A.C.P., Dean of the Medical School and former Surgeon General of the Army. General Kirk addressed the graduates of the Schools of Medicine and Nursing and presented their diplomas. Prior to the ceremonies, Dr. Byrd, President

of the University of Maryland, and members of the faculty of the Medical School gave a dinner in honor of General Kirk at the Hotel Belvedere.

#### Colonel Baker Awarded Legion of Merit

Colonel Benjamin M. Baker, F.A.C.P., Baltimore, has been awarded the legion of merit by General Douglas B. MacArthur for "exceptionally meritorious conduct in the performance of outstanding services in the South Pacific Area from April 20, 1942, to June 13, 1944."

The National Committee for Mental Hygiene has elected Major General Norman T. Kirk, F.A.C.P., The Surgeon General, as one of its six new members in recognition of his "unusual awareness of the importance of skilled psychiatric treatment in the Army."

Dr. Carl V. Moore, F.A.C.P., Associate Professor of Medicine, Washington University, St. Louis, Mo., is a recent appointee to the Army Epidemiological Board.

#### Army Medical Consultants Convene at White Sulphur Springs

The Service Command Consultants in Medicine and civilian physicians who are Consultants in Medicine to The Surgeon General and the Secretary of War convened at White Sulphur Springs, Va., October 30-31. Among those in attendance were Major General Norman T. Kirk, F.A.C.P., The Surgeon General, Colonel W. Paul Holbrook, F.A.C.P., Chief of Professional Service, Army Air Forces, Colonel Arden Freer, F.A.C.P., Chief of Professional Administrative Service, Lieutenant Colonel Francis R. Dieuaide, F.A.C.P., Chief of Tropical Disease Treatment Branch, Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant in Medicine to The Surgeon General, Colonel Walter Bauer, F.A.C.P., Consultant in Medicine, Eighth Service Command, Colonel E. V. Allen, Consultant in Medicine, Seventh Service Command and Lieutenant Colonel Joseph A. Hayman, Jr., F.A.C.P., Chief of Medical Service, Moore General Hospital, Swannanoa, N. C.

Lieutenant Colonel Phillip T. Knies, F.A.C.P., of Columbus, Ohio, Army member of the Interdepartmental Quarantine Commission, has been assigned as Army Quarantine Liaison Officer to The Surgeon General of the Army and is stationed in the Epidemiology Division, Preventive Medicine Service.

#### Wakeman Field Sanitary Area Dedicated

A model sanitary demonstration area was dedicated in October at Carlisle Barracks, Pa. It has been named Wakeman Field in memory of the late Colonel Frank B. Wakeman, F.A.C.P., who was Director of the Training Division, Office of The Surgeon General and former Instructor in the Department of Military Sanitation at Carlisle Barracks. Guest speakers stressed the importance of rigid sanitary measures in the field to prevent the spread of disease.

#### Army Trains Clinical Psychologists

An officers course in clinical psychology was inaugurated in October at the Adjutant General's School, Fort Sam Houston, Tex. The welcoming address was given by Lieutenant Colonel James B. Polka, Chief of the neuropsychiatry section of Brooke General Hospital, Fort Sam Houston, Tex., who represented Brigadier General George C. Beach, Jr., F.A.C.P., the hospital's Commanding General. Lieutenant Colonel Morton G. Seidenfeld, AGD, Chief Clinical Psychologist and Liaison with the Office of The Surgeon General, spoke on the duties and responsibilities of the clinical psychologist.

Representing The Surgeon General, Lieutenant Colonel Malcolm J. Farrell, MC, Assistant Director of the Neuropsychiatry Consultants Division, spoke on the relationship between the psychologist and psychiatrist in Army hospitals.

The new course will train officers who are clinical psychologists to deal with neuropsychiatric patients in Army hospitals. It includes a review of testing and interview technics, Army hospital procedures, types of problems encountered, diagnosis, clinical technics and therapeutic measures. A clinical psychologist is being detailed to the neuropsychiatric section of every Army hospital having a thousand or more beds.

---

#### GORGAS MEDAL PRESENTED TO JAMES J. SAPERO

Commander James J. Saperio (Associate), (MC), USN, is this year's recipient of the Gorgas Medal, for distinguished service as an Officer of the Medical Corps, U. S. Navy, in the field of malaria and preventive medicine. It was presented at the annual dinner of the Association of Military Surgeons, at New York, November 3, 1944. The award is sponsored by Wyeth Incorporated, and was established in memory of Surgeon General William Crawford Gorgas, whose work in preventive medicine made possible construction of the Panama Canal.

---

The Michigan State Medical Society announces its 1945 annual session to be held in Detroit, September 19-21.

---

Major George C. McEachern (Associate) has recently been made Chief of the Medical Service at the Army Air Force Regional and Debarkation Hospital, Hamilton Field, Calif. Major McEachern was previously Chief of the Rheumatic Fever Service at Buckley Field, Colo. He published his experiences in "The Treatment of Acute Rheumatic Fever with Penicillin," in the *Journal of the A. M. A.*, September 30, 1944.

---

Colonel Maurice C. Pincoffs, F.A.C.P., is now Chief of Professional Services, Southwest Pacific Area, U. S. Army.

---

Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, has been appointed on a Board of Honorary Consultants of the Army Medical Library by The Surgeon General.

---

Lieutenant Colonel Joseph Vander Veer (Associate), Philadelphia, is now Commanding Officer of the 364th Station Hospital, A. P. O. No. 322, Unit 1, San Francisco, Calif.

---

The Montreal Medico-Chirurgical Society conducted its 12th annual clinical convention in Montreal, October 16-21. This convention was conducted as a post-graduate course and was open to all practitioners not only in the Province of Quebec, but in the neighboring Provinces, as well as the adjoining States. There are four

other smaller clinical meetings held during the year for the same postgraduate teaching. Numerous Montreal institutions cooperate.

---

Commander Christopher C. Shaw, F.A.C.P., (MC), USNR, was commissioned a Lieutenant Commander in the Medical Corps of the U. S. Naval Reserve on July 28, 1940, from Bellows Falls, Vt., where he was engaged in the practice of internal medicine. He was ordered to active duty on May 19, 1941, and was first assigned to the U. S. Naval Hospital at Chelsea, Mass. One month later he was transferred to the U. S. Naval Station, Portsmouth, N. H., as Physician to the Naval Prison. From August 1 to September 30, 1941, he was a student at the School of Aviation Medicine, U. S. Naval Air Station, Pensacola, Fla., and remained there as a member of the faculty, Instructor in Cardiology. In early 1943, he was promoted to the rank of Commander and was designated a Flight Surgeon by the Bureau of Aeronautics, Navy Department. He became Senior Medical Officer at the U. S. Naval Auxiliary Air Station, Whiting Field, Fla., and later in the year was ordered to duty as Senior Medical Officer and Flight Surgeon of the Aircraft carrier, U. S. S. Solomons. He participated in the invasion on D-Day, and is at sea in the combat zones, Atlantic and/or Pacific. Since his entry on active duty, he has found time and the opportunity to publish articles on "Aviation Medicine" and "Heart Disease of Middle Age."

---

#### PHOTOS FROM DR. WHITE'S POSTGRADUATE COURSE

During the American College of Physicians Postgraduate Course in Cardiology, at Boston, October 2-7, under Dr. Paul White, F.A.C.P., many photographs were taken of the group at Massachusetts General Hospital and of various members of the faculty "in action," by Dr. Leslie French, F.A.C.P., Suite 215, 1726 Eye St., N. W., Washington, D. C. Dr. French announces that the prints are now available to any member of the course who may want them as mementos.

---

#### REGIONAL MEETINGS

The popularity and practicability of the regional meeting program of the College has been further demonstrated by the increasing interest and attendance at those recently conducted, as well as by the interest being shown in future scheduled meetings. Statistics of attendance are shown below for three of the recent meetings. It should be remembered, however, that different territories vary greatly in the number of College members and the number of medical officers in the Armed Forces. The regional meetings, therefore, are not comparable.

*New York Regional Meeting, October 20, 1944*—Officially 266 registered at the morning and afternoon programs; an evening attendance at the panel discussion on "Evaluation of Sulfa Drugs and Penicillin" of approximately 460, of whom more than two-thirds were Fellows and Associates of the College.

*Omaha, October, 23-27, 1944*—A combined War-Time Graduate Medical Meeting, certified as part of the Omaha Mid-West Clinical Society session. The total attendance at the meeting was 924, including 51 military officers from the surrounding posts. Twenty-one members of the American College of Physicians made presentations, as did also the Executive Secretary, Mr. E. R. Loveland, and the Associate Director of the American College of Surgeons, Dr. Malcolm T. MacEachern.

*Chicago Regional Meeting, November 4, 1944*—Embracing Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin.

	Fellows	Associates	Guests	Total
Army .....	18	14	39	71
Navy .....	3			3
U. S. Public Health Service .....		1	3	4
	—	—	—	—
Total, Servicemen .....	21	15	42	78
Civilians .....	182	37	75	294
	—	—	—	—
	<u>203</u>	<u>52</u>	<u>117</u>	<u>372</u>

Thirty-four States, the District of Columbia and Canada were represented. The primary reason for the national distribution of attendants was due to the fact that this Regional Meeting concluded the two-weeks' postgraduate course in Special Phases of Internal Medicine, under the auspices of the College in Chicago. There were officially registered in the course 157 physicians, with a number of additional visitors.

*Pittsburgh Regional Meeting, November 11, 1944*—Embracing Western Pennsylvania, Ohio and West Virginia.

	Fellows	Associates	Guests	Total
Army .....	4	1	5	10
Navy .....				
U. S. Public Health Service .....	—	—	—	—
Total, Servicemen .....	4	1	5	10
Civilians .....	78	23	56	157
	—	—	—	—
	<u>82</u>	<u>24</u>	<u>61</u>	<u>167</u>

The attendance was largely centered among members of the College from Western Pennsylvania, Ohio and West Virginia, but there was a scattered few from neighboring territory.

*Philadelphia, December 15, 1944*—Embracing Eastern Pennsylvania, New Jersey, and Delaware, in conjunction with the postgraduate course in Special Medicine at Philadelphia Institutions, December 4-15, and the annual meetings of the Committees and Regents of the College, December 15-16.

### PROGRAM

THOMAS M. McMILLAN, M.D., F.A.C.P.

General Chairman and Acting Governor for Eastern Pennsylvania

Friday, December 15, 1944

MORNING SESSION—9:30 a.m.—12:00 m.

Jefferson Medical College Hospital

1020 Sansom Street

(Clinical Amphitheatre, First Floor)

*Presiding Officer*

WILLIAM HARVEY PERKINS, M.D., F.A.C.P.

#### 1. Short Notes on the Rh Factor.

LOWELL ASHTON ERF, M.D., F.A.C.P., Associate in Medicine, Jefferson Medical College of Philadelphia.

2. Neurological Complications of Spinal Anaesthesia.  
HYMAN E. YASKIN, M.D. (by invitation), Demonstrator of Neurology,  
Jefferson Medical College of Philadelphia.
3. The Origin and Clinical Significance of Muscle Fasciculations.  
FRANCIS M. FORSTER, M.D. (by invitation), Assistant Professor of Neurology,  
Jefferson Medical College of Philadelphia, and  
BERNARD J. ALPERS, M.D. (by invitation), Professor of Neurology, Jefferson  
Medical College of Philadelphia.
4. Prolonged Fever.  
HOBART A. REIMANN, M.D. (by invitation), Professor of Medicine and  
Acting Head of Department of Experimental Medicine, Jefferson Medical  
College of Philadelphia.
5. Present Status of the Leukemia Problem.  
FRANKLIN R. MILLER, M.D. (by invitation), Associate Professor of Medicine,  
Jefferson Medical College of Philadelphia.
6. Some Psychological Factors in Obesity.  
ROBERT A. MATTHEWS, M.D. (Associate), Associate Professor of Psychiatry  
and Head of Department in absence of Colonel Baldwin L. Keyes,  
F.A.C.P., Jefferson Medical College of Philadelphia.
7. The Treatment of Rheumatic Chorea with Fever Therapy.  
EDWARD L. BAUER, M.D. (by invitation), Professor of Pediatrics, Jefferson  
Medical College of Philadelphia.

## LUNCHEON

(Buffet)

12:30 p.m.

## COLLEGE HEADQUARTERS

4200 Pine Street, Philadelphia, Pa.

AFTERNOON SESSION—2:45 p.m.

Ballroom

Benjamin Franklin Hotel

9th and Chestnut Streets

*Presiding Officer*

THOMAS M. McMILLAN, M.D., F.A.C.P.

## SYMPOSIUM ON RHEUMATIC FEVER

1. Some of the Clinical Problems of Rheumatic Fever.  
T. DUCKETT JONES, M.D. (by invitation), Assistant Professor of Medicine,  
Harvard Medical School; Director of Research, House of the Good  
Samaritan; Assistant Visiting Physician, Massachusetts General Hospital;  
Boston, Mass.
2. The Epidemiology of Rheumatic Fever.  
JOHN R. PAUL, M.D. (by invitation), Professor of Preventive Medicine, Yale  
University School of Medicine, New Haven, Conn.
3. The Council on Rheumatic Fever: Its Origin, Purposes and Present Status.  
H. M. MARVIN, M.D. (by invitation), Associate Clinical Professor of Medi-  
cine, Yale University School of Medicine; Acting Executive Secretary,  
American Heart Association, New Haven, Conn.

## 4. The Problem of Rheumatic Fever in the Armed Forces.

W. PAUL HOLBROOK, M.D., F.A.C.P., Colonel, (MC), AUS, Chief of the Professional Division, Office of the Air Surgeon, Washington, D. C.

## EVENING PROGRAM

Benjamin Franklin Hotel

9th and Chestnut Streets

6:30 p.m.—Reception and Cocktail Party

Betsy Ross Room, Mezzanine Floor

7:30 p.m.—Dinner (Informal)

Ballroom, Benjamin Franklin Hotel

*Toastmaster:* HENRY L. BOCKUS

Introduction of Distinguished Guests

(A few brief talks; no formal addresses)

*Memphis, January 25-26, 1945*—Embracing Tennessee, Arkansas, Louisiana and Eastern Texas; Dr. William C. Chaney, Chairman, Governor for Tennessee. The program for this meeting is not yet available but is in process of preparation with the assistance of the American College of Physicians. Governors for the participating states, namely, Dr. Edgar Hull, New Orleans, Governor for Louisiana, Dr. John G. Archer, Greenville, Governor for Mississippi; Dr. Oliver C. Melson, Little Rock, Governor for Arkansas; Dr. M. D. Levy, Houston, Governor for Texas. This meeting is expected to develop as one of the largest, most popular and really valuable regional meetings the College has conducted. It will be highlighted by the presence of several distinguished medical officers from the Army and Navy, including the Surgeons General or their official envoys. The program will be ready for distribution in late December, and will be mailed to all members and medical installations of the Army, Navy and Public Health Service in the territory mentioned. Physicians outside of the territory may obtain programs on request to the Executive Offices of the College. Cordial invitation is extended to every interested physician or medical officer, whether he be a member of the College or not.

*Oklahoma City, February 23, 1945*—Embracing Oklahoma, Kansas, Northwestern Texas, Missouri and Nebraska; Dr. Lea A. Riely, Chairman, Governor for Oklahoma. This will be the first regional meeting of its character in the Oklahoma City district. Chairman Riely is receiving the assistance and coöperation of the College Governors of the territory, including Dr. Harold Jones, Winfield, Governor for Kansas; Dr. M. D. Levy, Houston, Governor for Texas; Dr. Ralph Kinsella, St. Louis, Governor for Missouri; Dr. Warren Thompson, Omaha, Governor for Nebraska. While Nebraska has already held a regional meeting under date of October 26, in conjunction with the Omaha Mid-West Clinical Society, the State will also coöperate with the meeting in Oklahoma City. The Oklahoma City Internists Club will hold a meeting on February 22, to which members of the College will be invited. The Regional Meeting of the College follows on February 23, and members of the Oklahoma City Internists Club are invited, as are also medical officers of the Army, Navy and Public Health Service. This meeting has been planned for a considerable period of time and great care is being exercised in selection of subjects of especially timely interest given by recognized authorities in each field. The Chairman, Dr. Riely, has been a Governor of the American College of Physicians for about twenty years; his labors have always been characterized by the deepest interest in the welfare of the College and the medical profession; he is the dean of internists in his territory, and it is predicted that the Oklahoma members will rally to his assistance in organizing a memorable meeting in his honor.

The following letters from the Surgeons General Kirk and McIntire, which were published in the Bulletin of the War-Time Graduate Medical Meetings, indicate their interest in and approval of these meetings.

"The Army is very grateful to the Central Committee for the War-Time Graduate Medical Meetings it has been carrying on throughout the various parts of the United States in our Army hospitals. Both General Rankin and General Morgan, Consultants in Surgery and Medicine, Surgeon General's Office, feel that these meetings have been of great service as a morale builder, as well as informative to our medical officers serving at these various installations. It is their desire and mine that this work be continued for at least another year.

"Like you, I realize that the doctors in our hospitals have much more to do and this will increase as more battle casualties arrive from overseas and the number of medical officers available here at home to do the job declines. I feel that your Regional Chairmen through their contact with the commanding officers of these installations will be able to determine the advisability of scheduling meetings, their scope and the availability of doctor-hours in these hospitals to attend them.

"Many thanks again to you and your Committee and to the Regional Chairmen for the grand job that you have been doing for us."

NORMAN T. KIRK,  
Major General, U. S. Army,  
The Surgeon General.

"I have visited a great number of our institutions throughout the country during the past year and have had the opportunity of talking with numerous officers regarding the value of the War-Time Graduate Medical Meetings. The consensus is that they are of great help. I know from personal experience that they also have added value in bringing together the members of the medical profession in civil life and in the Services. In addition to this you are bringing to our institutions invaluable experience from qualified teachers throughout the nation and it can not but have a helpful affect in the war effort.

"I hope you will find it possible to continue these meetings throughout the coming year. As in the past, the Navy will co-operate in every way possible to make them a success."

ROSS T. MCINTIRE,  
Vice Admiral, U. S. Navy,  
The Surgeon General.

#### A. C. P. POSTGRADUATE COURSES

The continued popularity of the postgraduate courses offered by the American College of Physicians is again manifested by practically all courses being over-subscribed during the autumn of 1944. Readers may be interested in the following statistics of attendance.

#### Summary of Registration, A. C. P. Postgraduate Courses, Autumn, 1944

	Civilian Physicians	Service Medical Officers	Total	Grand Totals
<i>Course No. 1, Cardiology, Boston, Oct. 2-7.</i>				
Members, A. C. P.:				
Fellows .....	42	2	44	
Associates .....	11	3	14	
			—	
Non-Members .....	8	5	13	71
			—	



*Course No. 2, General Medicine, Portland,  
Oct. 9-14.*

Members, A. C. P.:			
Fellows .....	11	1	12
Associates .....	1	2	3
			—
			15
Non-Members .....	2	1	3
			—
			18

*Course No. 3, Internal Medicine, Minne-  
apolis, Oct. 9-14.*

Members, A. C. P.:			
Fellows .....	10	1	11
Associates .....	8	3	11
			—
			22
Non-Members .....	10	11	21
			—
			43

*Course No. 4, Allergy, New York City,  
Oct. 9-14.*

Members, A. C. P.:			
Fellows .....	16	3	19
Associates .....	5	2	7
			—
			26
Non-Members .....	23	10	33
			—
			59

*Course No. 5, Internal Medicine, Chicago,  
Oct. 23-Nov. 4.*

Members, A. C. P.:			
Fellows .....	47	12	59
Associates .....	18	10	28
			—
			87
Non-Members .....	38	54	92
			—
			179

*\* Course No. 6, Special Medicine, Phila-  
delphia, Dec. 4-15.*

Members, A. C. P.:			
Fellows .....	25	7	32
Associates .....	7	5	12
			—
			44
Non-Members .....	8	25	33
			—
			77*
	—	—	—
	290	157	447
	==	==	==

\* Advanced Registration, Not Final.

## Tentative Roster, Spring, 1945

Full announcement of the roster will appear in the next issue of this journal. At the present time, it is planned to give five courses: Cardiovascular Diseases; Gastrointestinal Diseases; Internal Medicine; Clinical Medicine, with Special Emphasis upon the Hematological Viewpoint; Applications of Psychiatry to the Practice of Internal Medicine.

Fees and other regulations will be the same as heretofore. Medical officers of the Armed Forces will be admitted free; members of the College will pay a tuition fee of \$20.00 per week; non-members, \$40.00 per week.

---

The Massachusetts General Hospital, Boston, through its general Executive Committee, has established a Staff Memorial Fund to which contributions may be made in honor of the memory of any staff member. The plan grew out of a wish to honor Dr. William B. Breed, F.A.C.P., who died August 21. Dr. Breed had been a member of the general Executive Committee and had served the Massachusetts General Hospital for 25 years.

---

The faculty and alumni of Western Reserve University School of Medicine on September 25, honored their former Dean and former Professor of Pharmacology, Dr. Torald H. Sollmann, F.A.C.P., at a dinner. They presented him with a silver plaque in recognition of his distinguished services. Dr. Sollmann was associated with Western Reserve University for nearly 50 years. He is now Chairman of the Council on Pharmacy and Chemistry of the American Medical Association.

---

Dr. Samuel E. Thompson, F.A.C.P., Kerrville, has resigned as a member of the Texas State Board of Health.

---

Dr. John Walker Moore, F.A.C.P., Dean of University of Louisville School of Medicine, was made president-elect of the Association of American Medical Colleges at its annual meeting in Detroit, October 23-25. Dr. William S. McEllroy, F.A.C.P., Dean of the University of Pittsburgh School of Medicine was elected vice-president. Dr. Walter A. Bloedorn, F.A.C.P., Dean of George Washington University School of Medicine, Washington, D. C., and Dr. Wilburt C. Davison, F.A.C.P., Dean of Duke University School of Medicine, Durham, N. C., were elected members of the Executive Council of the Association, succeeding Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, and Dr. Russell H. Oppenheimer, F.A.C.P., Dean of Emory University School of Medicine, Atlanta.

---

COLONEL OTIS O. BENSON, JR., HONORED

Colonel Otis O. Benson, Jr. (Associate), (MC), U. S. Army, has been awarded the legion of merit by the War Department, his citation reading, "In his capacity as Chief of Aero Medical Research at Wright Field from September 6, 1940, to July 15, 1943, he was responsible for successfully developing, testing and standardizing all items of medical equipment used in connection with military aviation. His professional skill and organizing ability made it possible for his unit, during a period of rapidly changing requirements, to succeed in applying previously known principles of aviation medicine to the practical situations of modern warfare and solving new problems arising from unexpected developments in aerial combat."

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., addressed the Fairfield County Medical Association in Stamford, Conn., October 4, on "The Future of Prepayment Medical Plans."

---

On November 2, Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered the 17th annual Pasteur Lecture of the Institute of Medicine of Chicago. Dr. Strecker's subject was "War Psychiatry and Its Influence on Post-War Psychiatry and Civilization."

---

The late Dr. Andrew P. Biddle, F.A.C.P., Detroit, who died on August 2, 1944, bequeathed approximately \$40,000.00 to the Michigan State Medical Society, of which he had formerly been president, for use in the furtherance of its program of postgraduate medical education.

---

Dr. Oswald T. Avery, Phillips Medalist of the American College of Physicians in 1932, was awarded the Gold Medal of the New York Academy of Medicine "for distinguished service in medicine" at a meeting on October 5. The presentation was made by Dr. Arthur F. Chace, F.A.C.P., President of the Academy.

---

Dr. Edward B. Krumbhaar, F.A.C.P., Professor of Pathology, University of Pennsylvania School of Medicine and Graduate School of Medicine, has been elected an honorary Fellow of the Royal Society of Medicine, London.

---

Dr. Kenneth E. Appel, F.A.C.P., Philadelphia, was recently elected president-elect of the Pennsylvania Psychiatric Society.

---

The Southern Medical Association conducted its 38th annual meeting at St. Louis, Mo., November 13-16. Among those on the program were: Col. Howard A. Rusk, F.A.C.P., "New Horizons in Medicine"; Capt. Alphonse McMahon, F.A.C.P., "Civilian Tropical Disease Problems Following Demobilization"; Dr. Charles F. Mohr, F.A.C.P., Baltimore, "Results of Penicillin Treatment in Neurosyphilis"; Dr. Harry S. Bernton, F.A.C.P., Washington, D. C., "Castor Bean Sensitiveness"; Dr. Cornelius O. Bailey, F.A.C.P., Los Angeles, "Post-war Medical Education."

---

The Medical Society of Virginia held its annual meeting in Richmond recently, with an attendance of 570 doctors. Dr. H. B. Mulholland, F.A.C.P., of Charlottesville, succeeded to the presidency. Dr. Philip S. Smith, F.A.C.P., of Abingdon, is a vice-president, and Dr. C. Lydon Harrell, F.A.C.P., of Norfolk, is a Councilor from the Second District. The Society will hold its 1945 session in Roanoke.

---

Dr. Robert H. Bayley, F.A.C.P., has been appointed Professor of Clinical Medicine and Vice Chairman of the Department of Medicine of the University of Oklahoma School of Medicine. Dr. Bayley for several years was Associate Professor of Medicine at the Louisiana State University School of Medicine, New Orleans.

---

The Oklahoma City Clinical Society conducted its 14th annual fall clinical conference in Oklahoma City, October 23-26. Among the guest lecturers were the following: Dr. Tinsely R. Harrison, F.A.C.P., Dallas, Tex., "Abdominal Disorders Simulating Coronary Artery Disease" and "Recent Concepts of Hypertension";

Dr. Ralph A. Kinsella, F.A.C.P., St. Louis, Mo., "Arthritis" and "Etiology, Diagnosis, and Treatment of Acute Dilatation of the Heart"; Dr. Bruce K. Wiseman, F.A.C.P., Columbus, Ohio, "Primary Atypical or Virus Pneumonia" and "The Leukemias."

A large proportion of the Fellows of the College in the Oklahoma City district contributed also to the program.

---

The Dallas Southern Clinical Society will hold its 15th annual spring clinical conference at Hotel Adolphus, Dallas, March 19-22, 1945. Among the guest speakers will be Dr. J. Arnold Bargaen, F.A.C.P., Rochester, Gastro-enterology; Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, Internal Medicine; Dr. William Henry Sebrell, Jr., F.A.C.P., U. S. Public Health Service, Washington, D. C., Basic Science; and Dr. George W. Thorn, F.A.C.P., Boston, Mass., Internal Medicine.

---

Dr. Irvine H. Page, F.A.C.P., for the past seven years Director of the Eli Lilly Laboratory for Clinical Research, Indianapolis, will become Director of Research at the Cleveland Clinic, Cleveland, on January 1.

---

Dr. Oscar O. Miller, F.A.C.P., Louisville, was inducted into the presidency of the Kentucky State Medical Association at its last annual meeting in Lexington.

---

Dr. Carl V. Moore, F.A.C.P., Associate Professor of Medicine, Washington University School of Medicine, St. Louis, was among the first of a group of visiting professors to the University of Louisville School of Medicine under a grant for this purpose by the Commonwealth Fund.

---

Dr. John H. Musser, F.A.C.P., and Dr. Julius L. Wilson, F.A.C.P., both of New Orleans, are president and medical consultant, respectively, of the newly chartered and organized Tuberculosis Association of New Orleans.

---

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, gave the commencement address before the University of Utah School of Medicine, Salt Lake City, on September 10. Dr. Parran received the honorary degree of Doctor of Science. This is the first graduation exercises of this new four-year medical school.

---

Brigadier General Eugen Reinartz, F.A.C.P., (MC), U. S. A., was installed as President of the Aero Medical Association of the United States at its meeting in St. Louis on September 4.

---

Dr. George H. Anderson, F.A.C.P., Spokane, has been elected president-elect of the Washington State Medical Association for the coming year.

---

Dr. Lewis G. Allen, F.A.C.P., Kansas City, Kan., has succeeded to the presidency of the Radiological Society of North America.

---

Dr. Lyell C. Kinney, F.A.C.P., San Diego, has succeeded to the presidency of the American Roentgen Ray Society.

Dr. George M. Lewis, F.A.C.P., New York, addressed the New York State Association of Public Health Laboratories at Albany, November 17, on "Clinical and Immunological Aspects of Fungus Infection."

Dr. Frank R. Menne, F.A.C.P., has resigned as Professor and Head of the Department of Radiology at the University of Oregon Medical School, Portland, with which institution he has been associated for 28 years.

Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., has been made an honorary member of the Sociedad Chilena de Tisiologia.

Under the presidency of Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., the American Public Health Association conducted its second war-time public health conference and its 73rd annual business meeting in New York, October 2-5.

The September issue of the *Mississippi Doctor* was dedicated to Dr. Underwood, who is the Mississippi State Health Officer.

Colonel Neely C. Mashburn, F.A.C.P., has become Surgeon of the A. A. F. Training Command, Fort Worth, Tex., succeeding Brigadier General Charles R. Glenn, who has been appointed Deputy Air Surgeon of the Army Air Forces, headquarters in Washington, D. C.

#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 1 (Maine, New Hampshire, Vermont, Massachusetts) and REGION No. 2 (Connecticut, Rhode Island)—New England Committee for War-Time Graduate Medical Meetings—Dr. W. R. Ohler, Chairman; Dr. L. E. Parkins, Secretary; Dr. S. B. Weld, Dr. A. M. Burgess, Dr. C. S. Keefer, Dr. F. T. Hill, Dr. J. P. Bowler, Dr. B. F. Cook, Executive Committee members

*Station Hospital, Dow Field, Bangor, Maine*

December 21 Head, Spine and Nerve Injuries

*Dispensary, U. S. Naval Air Station, Brunswick, Maine*

December 21 Burns and Reconstruction Surgery

*Station Hospital, Fort Williams, Portland, Maine*

December 21 The Skin

*Station Hospital, Presque Isle, Maine*

December 21 Stomach, Biliary Tract, Intestinal Disorders

*Dispensary, U. S. Naval Construction Training Center, Quoddy Village*

December 21 Pilonidal Sinus and Common Diseases of the Anus and Rectum

*Station Hospital, Grenier Field, Manchester, New Hampshire*

December 20 Peripheral Vascular Disease

*U. S. Naval Hospital, Portsmouth, New Hampshire*

December 21 Diarrheal Diseases

*Boston Area Station Hospital, Waltham, Massachusetts*

December 21 The Use of Penicillin and the Sulfa Drugs

*U. S. Naval Hospital, Chelsea, Massachusetts*

December 21 Blood Dyscrasias and Transfusions

*Lovell General Hospital, Fort Devens, Massachusetts*

December 21 The Pneumonias and Other Respiratory Infections

*Station Hospital, Camp Edwards, Massachusetts*

December 21 The Psychoneuroses and Their Management

*Cushing General Hospital, Framingham, Massachusetts*

December 21 Contagious Diseases and Complications

*Station Hospital, Camp Myles Standish, Taunton, Massachusetts*

December 21 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

*U. S. Marine Hospital, Brighton, Massachusetts*

December 21 Acute Infections of the Central Nervous System

*Station Hospital, Westover Field, Chicopee Falls, Massachusetts or U. S. Naval Convalescent Hospital, Springfield, Massachusetts*

December 21 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

*Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island*

December 21 Joint Injuries

*U. S. Naval Hospital, Newport, Rhode Island*

December 21 Fractures of Extremities

*Station Hospital, Bradley Field, Windsor Locks, Connecticut*

December 21 Fractures of Extremities

*Air Corps Station Hospital, New Haven, Connecticut*

December 21 Chest and Abdominal Injuries

*Station Hospital, Fort H. G. Wright, Fishers Island, New York*

December 21 Acute Abdominal Emergencies

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

*U. S. Naval Hospital, Philadelphia, Pennsylvania*

January 26 Common Mistakes in the Diagnosis of Treatment of Gastrointestinal Diseases—Dr. Henry L. Bockus

REGION No. 8 (Western Pennsylvania, Ohio)—Dr. C. A. Doan, Chairman; Dr. P. G. Smith, Dr. F. M. Douglass.

*Crile General Hospital, Cleveland, Ohio*

January 23 Polycythemia—Dr. Russell H. Haden

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman;  
Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M.  
Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

*Camp McCoy, Wisconsin*

January 3 Peptic Ulcer and Gastritis—Dr. Carl W. Eberbach

January 17 Chemotherapy (Present Status)—Dr. Harry Beckman

January 31 Gall Bladder and Liver Disease—Dr. Erwin R. Schmidt

*Truax Field, Wisconsin*

January 3 Chronic Chest Diseases and Disease of the Larynx—Dr. John D. Steele

January 17 Head and Spine Injuries—Dr. T. C. Erickson

January 31 Allergic States—Dr. Theodore L. Squier

*Mayo General Hospital, Galesburg, Illinois*

January 3 Plexus and Peripheral Nerve Injuries

January 17 Dermatological Diseases

January 31 Burns and Plastic Surgery

*Vaughan General Hospital, Illinois*

January 3 Burns and Plastic Surgery

January 17 Malignancies in the Army Age Group—Medical X-Ray and Surgical  
Diagnosis and Treatment

January 31 Endocrinology

*Camp Ellis, Illinois*

January 3 Endocrinology

January 17 Virus and Rickettsial Diseases—Medical and Neurological Diseases and  
Treatment

January 31 Psychosomatic Medicine

*Chanute Field, Illinois*

January 3 Heart Disease and Allied Conditions

January 17 Repair of Bone in Fractures and Diseases

January 31 Arterial Vascular Disease—Traumatic Lesions

REGION No. 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr. F. D. Dickson, Chair-  
man; Dr. O. P. J. Falk, Dr. H. H. Turner.

*Station Hospital, Rosecrans Field, St. Joseph, Missouri*

January 11 Chemotherapy  
Trauma of the Abdomen

*Regional Hospital, Fort Riley, Kansas*

January 11 Allergy  
Nutritional Deficiency Diseases

January 25 Clinical Psychiatry  
Neurology

*Station Hospital, Army Air Field, Great Bend, Kansas*

- January 4 Shock, Burns and Blood Derivatives  
Clinical Psychiatry  
January 18 Venereal Diseases and Urology  
Anesthesia

*Winter General Hospital, Topeka, Kansas*

- January 18 Gastrointestinal Diseases—Dr. Carl R. Ferris  
General Surgery—Dr. Claude J. Hunt

POSTGRADUATE COURSE IN MEDICINE BY WOMAN'S MEDICAL COLLEGE OF  
PENNSYLVANIA

Dr. William G. Leaman, Jr., F.A.C.P., Professor of Medicine at the Woman's Medical College of Pennsylvania, has announced the following lecture schedule for the Postgraduate Course in Medicine at the Woman's Medical College of Pennsylvania for the latter part of 1944 and the early part of 1945. The average attendance has been 45. This course has been conducted each winter.

November 22, 1944—7:00 to 9:00 p.m. Coronary Disease; Digitalis Therapy. William D. Stroud, F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

December 6, 1944—7:00 to 9:00 p.m. Recent Trends in the Treatment of Cardiovascular Disease. William G. Leaman, Jr., F.A.C.P., Professor of Medicine, and Samuel Bellet (Associate), Associate Clinical Professor of Medicine, Woman's Medical College of Pennsylvania.

January 3, 1945—7:00 to 9:00 p.m. Recent Advances in Hematology. Leandro M. Tocantins (Associate), Associate Professor of Medicine, Jefferson Medical College.

January 17, 1945—7:00 to 9:00 p.m. Recent Advances in Our Knowledge of Kidney Disease. Edward Weiss, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

January 31, 1945—7:00 to 9:00 p.m. Practical Aspects of Essential Hypertension. Edward Weiss, F.A.C.P.

February 14 and 28 will be devoted to Gastrointestinal Tract; March 14 to Endocrinology; March 28, April 11 and 25, to Parasitology and Tropical Medicine. The speakers for these occasions will be announced early in January.

BRIGADIER GENERAL SIMMONS RECEIVES WALTER REED MEDAL

On November 15, 1944, at the annual meeting of the American Society of Tropical Medicine, in St. Louis, Mo., the Society presented to Brigadier General James Stevens Simmons, F.A.C.P., U. S. A., Chief, Preventive Medicine Service, Office of The Surgeon General, U. S. Army, the Walter Reed Medal in recognition of meritorious achievement in tropical medicine, and for outstanding work in safeguarding the health of American troops.

The Walter Reed Medal was established by the Society in 1934 to be awarded periodically in recognition of meritorious achievement in tropical medicine by an individual or an institution.



The medal has been awarded on four previous occasions. In 1936, one medal was awarded posthumously to Major Walter Reed for his experimental work on yellow fever and another to the Rockefeller Foundation for its study and control of yellow fever. In 1939 the award was made to Dr. William B. Castle, F.A.C.P., of Harvard University and in 1940 to Dr. Herbert Clark of the Gorgas Memorial Laboratory in Panama. In 1942 two medals were awarded, one posthumously to Dr. Carlos J. Finlay for his work on yellow fever and the other to The United States of Brazil "for outstanding work in the eradication of *Anopheles gambiae* in Brazil."

At the recent meeting, General Simmons was also chosen as "President Elect" of the American Society of Tropical Medicine.

---

### SPECIAL NOTICES

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at Michael Reese Hospital by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each week, starting Wednesday, February 14 for 12 weeks, from 7:00 to 9:00 p.m.

Further information and a copy of the program may be obtained on application to the Cardiovascular Department, Michael Reese Hospital.

---

The Executive Board of the American Public Health Association announces that the Third Wartime Conference and 74th Annual Meeting, and meetings of related organizations, will be held in Chicago, Illinois, the week of September 17, 1945, with headquarters in the Hotel Stevens.

At its Annual Meetings, this professional society of public health workers brings together the health officials of the Western Hemisphere for discussion of local, national and international health problems. The Chicago program will cover subjects of interest to health officers, public health nurses, laboratory workers, nutritionists, vital statisticians, engineers, child and maternal health specialists, health educators, public health dentists, epidemiologists, industrial hygienists and others working in the broad field of health protection and promotion.

The related organizations will include the American School Health Association, the Conference of State and Municipal Public Health Engineers, of Public Health Nursing Directors, of Professors of Preventive Medicine, of State and Provincial Public Health Laboratory Directors, of State Directors of Public Health Education, and of Industrial Health Consultants.

The Illinois Committee in charge of local arrangements will be headed by Dr. Herman N. Bundesen, President, Chicago Board of Health, and Dr. Roland R. Cross, State Director of Public Health, Springfield, Illinois, Co-Chairmen.

The headquarters office of the American Public Health Association is located at 1790 Broadway, New York 19, N. Y. Reginald M. Atwater, M.D., is Executive Secretary.

## OBITUARIES

## DR. ARTHUR MONTELL SMITH

On July 21, 1944, Dr. Arthur Montell Smith, F.A.C.P., died at the Merritt Hospital, in Oakland, California. Dr. Smith was born in Topshan, Maine, on March 18, 1872.

Before the age of 20 he came to California with his family, settling in San Jose, California. He began his medical studies with Dr. Bangs in San Jose and later entered the Cooper Medical College in San Francisco, receiving his M.D. degree in 1899. Shortly after graduation he began the practice of medicine at Merced, California, where he practiced for about five years. His next move was to Oakland, California where he began practice first as a general practitioner, later doing postgraduate work in eastern medical centers and preparing himself for the specialty of internal medicine. He served as a Captain in the Medical Corps during World War I and was stationed at Camp Kearny, later serving overseas. He served as Chief of the Medical Staff of the Samuel Merritt Hospital in Oakland for over 30 years. He was also at one time Superintendent of the Alameda County Hospital, and during his early career he was Health Officer for the City of Oakland. At one time he was on the California State Board of Medical Examiners.

His medical society memberships included the Alameda County Medical Society, California State Medical Society, and California Academy of Medicine. He was a Fellow of the American Medical Association and also a Fellow of the American College of Physicians since 1922.

Dr. Smith had retired from active practice in 1943. He leaves a widow, Mrs. Laura Luers Smith, and a daughter, Marian, who is the wife of Major Paul Sampson of the Army Medical Corps.

ERNEST H. FALCONER, M.D., F.A.C.P.,

Governor for Northern California

## DR. LINDSAY STEPHEN MILNE

Dr. Lindsay Stephen Milne, F.A.C.P., of Kansas City, Mo., passed away at his home on September 17, 1944, following an illness of several months.

Dr. Milne was born in Montrose, Scotland, May 8, 1883. He graduated from the Montrose Academy in 1899, and obtained his Medical Degree at the University of Edinburgh, Scotland, in 1904. He was a Fellow of the Royal College of Physicians of Scotland. For a time, he was Instructor in the Departments of Pathology and Internal Medicine at his Alma Mater.

Dr. Milne was engaged in research work for a considerable period of time in Panama, Costa Rica, Brazil and South Africa. In 1908, he became affiliated with the Russell Sage Foundation and later with the Rockefeller

Institute for Medical Research, and was engaged in research in Pathology, chiefly on the liver. In 1912, he went to Kansas City, Mo., to head the Department of Medicine and to become Professor of Internal Medicine at the University of Kansas School of Medicine. He served as a Captain in the Medical Corps of the Army during World War I, having been stationed at Camp Funston, Kan., on the Mexican Border, Camp McPherson, Ga., and with the A.E.F. in France, where he was the Commanding Officer of Base Hospital No. 28, the Kansas City Unit. He was advanced to the rank of Colonel.

Dr. Milne practiced medicine in Kansas City until July, 1944, and had served in recent years as Attending Physician to the Kansas City General, Research and St. Luke's Hospitals. He was a Diplomate of the American Board of Internal Medicine and was the author of several published papers.

A fellow townsman has written: "In his thirty years residence in Kansas City, Dr. Lindsay Stephen Milne had established himself as an important factor in the city's medical life. To a rare degree, he combined thorough medical training, fine judgment and rare human sympathy. His death removes from this community not only a distinguished man of medicine, but a great human being."

#### DR. HARRY ALLEN RICHTER

Dr. Harry Allen Richter, F.A.C.P., Chicago, died July 8, 1944, of carcinoma; aged, 47. Dr. Richter was born in Chicago on August 27, 1896. He graduated from Northwestern University Medical School in 1923, and later did postgraduate work at the Massachusetts General Hospital, Boston. He was Associate in Medicine at Loyola University School of Medicine; Cardiologist at the St. Francis and Swedish Covenant Hospitals; and Associate Staff Physician, Cook County Hospital.

Dr. Richter was the former historian of the Chicago Medical Society; he was a member of the Illinois Medical Society, American Heart Association and American Therapeutic Society; a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1940. He had published a number of medical articles.

#### DR. EDWARD SHEARMAN McSWEENEY

Dr. Edward Shearman McSweeney died of coronary thrombosis on September 17, 1944. Dr. McSweeney was one of the charter Fellows in The American College of Physicians and led a long and active medical life in New York City.

He was born in 1877; attended St. Francis Xavier College; M.D., 1897, and D.P.H., 1921, Bellevue Hospital Medical College; postgraduate work, 1900-01, University of Berlin, University of Munich and private courses in Vienna. In his early career he was partially interested in surgery, and was

for the period 1901-05, Surgeon, O.P.D., St. Vincent's Hospital, New York City; at the same time, however, he was Demonstrator in Anatomy at New York University Medical School and Physician to the Foundling Hospital. He was at one time President of the Medical Board, St. John's Hospital, and Consultant to the Loomis Sanatorium and Grasslands Hospital, and member of the Medical Board of the Stony Wold Sanatorium; also member of the Medical Board at Gabriel's Sanatorium and the Workmen's Circle Sanatorium (Liberty). He later became Director of the Tuberculosis Preventorium and Trustee of the Potts Memorial Hospital; he had been also Medical Superintendent of the Sea View Hospital in Castleton Corners, N. Y., and the Tuberculosis Sanatorium of the New York City Department of Health in Otisville, N. Y.; he was also Medical Director of the New York Telephone Company and Consulting Physician to the Mary Immaculate Hospital, Jamaica, and St. John's Long Island City Hospital, Long Island City.

He was a former President of the New York Celtic Medical Society and of the Bellevue Alumni Society; former Secretary-Treasurer of the American Sanatorium Association; member of the New York County and State Medical Societies, New York Academy of Medicine, Harvey Medical Society, New York State Society of Industrial Physicians, New York Tuberculosis Association, National Tuberculosis Association, American Association for Thoracic Surgery, American Trudeau Society; Fellow, American Medical Association; Fellow of the American College of Physicians (charter member), June 25, 1915; Diplomate, American Board of Internal Medicine; died September 17, 1944, of coronary thrombosis; aged 66.

Dr. McSweeny was very actively interested in medical matters up until the time of his death.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

#### DR. EDWARD C. GAGER

Dr. Edward C. Gager, F.A.C.P., was born in Saint Paul, December 16, 1882. He graduated from Central High School in 1900 and received his M.D. degree from the University of Minnesota Medical School in 1905.

He began practicing in Chamberlain, South Dakota, and later moved to North Branch, Minnesota. He began practice in Saint Paul in 1908 and became interested in dermatology, taking postgraduate work in Paris, Vienna, and the Postgraduate Medical Hospital in New York. Then for several years he was Assistant Professor of Dermatology of the University of Minnesota Medical School, and later Chief of the Venereal Disease Clinic of the Wilder Dispensary as well as Attending Dermatologist of Ancker Hospital.

Dr. Gager was a member of the Ramsey County Medical Society, the Minnesota State and American Medical Associations, the American College of Physicians, the Minnesota Dermatological Society, and The American Medical Association.

He died July 29, 1944, at the age of sixty-two of acute myocardial failure following an operation for intestinal obstruction due to gallstones in the ileum. He is survived by three brothers, Paul C. of Memphis, Tennessee, Alfred R. of State College, Pennsylvania, and Ray R. of Saint Paul.

## REAR ADMIRAL CHARLES ST. JOHN BUTLER

### MEDICAL CORPS, USN, RETIRED

In the death of Rear Admiral Charles St. John Butler, F.A.C.P., on October 7, 1944, at his home in Bristol, Tennessee the Medical Corps of the Navy lost one of its most eminent members and the American College of Physicians, one of its most distinguished Fellows. Admiral Butler was no ordinary individual but one who at all times at once arrested the attention. Large and massive in stature, his intellect was on a proportionate scale with his physical appearance. His strongly marked and emphatic personality made him what journalists are fond of referring to as a "Stormy Petrel." It must not be supposed, however, from this description that there was anything forbidding or ungracious about him. On the contrary, he was kindness itself and a most engaging and considerate physician and administrator, but a love of truth and unflinching integrity so ruled him that he was most outspoken in the defense of any scientific fact, or of any measure to better conditions which he felt were not right. He had the true zeal of a reformer and it was this characteristic which played a part in his great success as a medical administrator.

In the Virgin Islands, he was Commanding Officer of the Naval Hospital and Health Administrator of the islands and as head of the Public Health Service in Haiti, he was outstandingly successful. An eminent authority on tropical medicine has declared that Admiral Butler's work in the Virgin Islands in eliminating tropical disease was, on a small scale, as remarkable as that done by General Gorgas in Panama. In Haiti Admiral Butler is regarded as the man who did the most in the conquest of tropical disease in that island.

Admiral Butler will be remembered as connected with two interesting problems of tropical medicine and medical history. One was the unity of yaws and syphilis and the other, the controversy as to the Old World origin of syphilis as against the origin in the Americas. He was a strong believer in the unity of syphilis and yaws and a strong advocate of the theory that syphilis had existed in Europe prior to the Columbian voyages. On both of these subjects, Admiral Butler wrote and lectured extensively and his pronounced and vigorous views have some of the force and character of the

old Renaissance scientists. He was a learned and ingenious controversialist and his sound scholarship made his views and arguments difficult to overthrow.

He was a notable teacher of tropical medicine. The Medical Corps of our Navy and the Medical Corps of the Army were pioneers in tropical medicine in the United States, and the Naval Medical School for the first two decades of the present century was a principal center for the teaching of this specialty in this country. In the present war the success or failure of naval or amphibious operations in the tropics has depended many times on the knowledge of tropical diseases and the methods of their prevention. The training given our medical officers by men like Admiral Butler did much to enable them to cope successfully with these threats and protect our fighting forces from enemies more deadly even than armed men. Admiral Butler himself, must have realized this and have taken pleasure in the thought that he had so helped the Medical Corps of the Navy in the world's greatest war even though age had placed him in retirement.

Admiral Butler was born in Bristol, Tennessee, March 1, 1875, educated at Kings College, Emory and Henry College at Emory, Virginia and graduated in medicine from the University of Virginia in 1897. He was commissioned Assistant Surgeon in the Navy November 8, 1900. His first duty was on the old United States Fisheries Commission steamer *Albatross*, on which he served as Medical Officer and where his strong bent for scientific investigation was also utilized. Throughout his career, he served in many parts of the world and held many important positions. He was an instructor in bacteriology and tropical medicine at the U. S. Naval Medical School; Commanding Officer of the Naval Medical School and at one time acted as Professor of Medicine in the George Washington University School of Medicine. In addition to the posts which have been previously mentioned in the Virgin Islands and in Haiti, he had been Commanding Officer of the Naval Medical Supply Depot, Brooklyn, N. Y., the Naval Medical Center in Washington, D. C., and President of the Board of Medical Examiners for Officers of the Medical Corps. He served on the National Research Council and he was a member of many scientific and professional societies, including the Association of Military Surgeons, the American Academy of Tropical Medicine, American Society of Tropical Medicine and the Society of American Bacteriologists. He was the author of many professional papers and of a book, "Syphilis Sive Morbus Humanus," dealing particularly with the history of syphilis and yaws.

His death is a distinct loss in the fields of tropical medicine and medical history and to his many friends throughout the world.

ROSS T. McINTIRE, F.A.C.P.,  
Vice Admiral, (MC),  
A.C.P. Governor for the U. S. Navy

## DR. EDWARD MELVIN GREEN

Dr. Edward Melvin Green, M.D., F.A.C.P., of Harrisburg, Pennsylvania, former Superintendent of the Harrisburg State Hospital, died on September 30, 1944. Dr. Green was 77 years of age, was born in Washington, Georgia, July 10, 1867. He graduated from Centre College in 1887, receiving his Master of Arts degree from that institution in 1890, the same year in which he received his degree of Doctor of Medicine from the University of Pennsylvania School of Medicine. He did post-graduate work at the Jefferson Medical College Hospital in Philadelphia; Manhattan State Hospital in New York; and from 1891 to 1895 was assistant physician at the Eastern Kentucky State Hospital for the Insane. During 1896 and 1897 he was Physician in Charge of the Oklahoma State Hospital; from 1901 to 1917 he was on the Staff of the Milledgeville State Hospital, Georgia, and left a clinical directorship at that hospital in 1917 to become Superintendent of the Harrisburg State Hospital, which position he held until his retirement in 1934. Following his retirement he engaged in consultation practice, and was consultant at the Harrisburg Polyclinic and the Lancaster County Hospitals, and was Director of the Neuropsychiatric Service at the York (Pennsylvania) Hospital for several years. He was a Fellow of the American Psychiatric Association, the American College of Physicians and the American Medical Association. He was the author of numerous papers, several of which on psychoses in negroes attracted wide attention. In 1942, in spite of his advancing years, he returned to aid in the work of the Harrisburg State Hospital, and throughout the War period was an active member of the Medical Advisory Board of the Pennsylvania Selective Service. A physician of high ideals and gracious Christian character, possessed in a marked degree of the quality of dignity, imperturbability and gentleness, he maintained the high standards of his profession, and was held in great respect in the community in which he lived, and where he was active in his support of worth while public projects. He is survived by his wife, Ann C. Green; and two sons—Lieutenant Edward M. Green, Jr., USNR; and Louis C. Green, Ph.D., on the teaching Staff at Bryn Mawr College. Interment was at Dr. Green's boyhood home, Danville, Kentucky.

H. K. PETRY, M.D., F.A.C.P.

# ANNALS OF INTERNAL MEDICINE

## AUTHOR INDEX

Volume 21, July-December, 1944

- |   |      |   |     |
|---|------|---|-----|
| ALBRECHT, F. K. The Use of Benz-<br>drine Sulfate in Obesity.....   | 983  | Dietary Therapy of Cirrhosis of the<br>Liver.....   | 848 |
| ALEXANDER, J. Rôles of Medicine and<br>Surgery in the Management of Bron-<br>chiectasis.....  | 565  | BRAMWELL, C. and J. T. KING. The<br>Principles and Practice of Cardiology.<br><i>Rev.</i> .....   | 917 |
| APPLEBAUM, I. L. Serum Amylase in<br>Mumps.....   | 35   | BRONSTEIN, L. H., H. W. POTTER and<br>—. Some Clinical Characteristics of<br>Mumps, and the Effect of Belladonna<br>in Treatment: A Study Made at the<br>Station Hospital, Fort George G.<br>Meade, Maryland..... | 469 |
| ARMSTRONG, C. D., W. M. M. KIRBY<br>and—. Sarcoidosis with Uveoparotid<br>Fever. <i>Case Rep.</i> .....   | 475  | BRONSTEIN, L. H., H. W. POTTER, R. D.<br>REID and—. Meningococcemia with-<br>out Meningitis; A Study Made at the<br>Station Hospital, Fort George G.<br>Meade, Maryland.....                                      | 200 |
| ARROWSMITH, W. R., B. BINKLEY and<br>C. V. MOORE. Fatal Agranulocyto-<br>sis Following the Intraperitoneal Im-<br>plantation of Sulfanilamide Crystals.<br><i>Case Rep.</i> .....                     | 323  | CHAPMAN, C. B. and S. L. ROBBINS.<br>Patent Ductus Arteriosus with Pul-<br>monary Vascular Sclerosis and Cya-<br>nosis. <i>Case Rep.</i> .....  | 312 |
| ASKEY, J. M. The Dietary Factor in<br>the Etiology of Pernicious Anemia..   | 402  | CLARE, F. B., C. H. CRESS and E. GELL-<br>HORN. Leukocytosis and the Sym-<br>pathetico-Adrenal System.....  | 653 |
| ATKINSON, M. Migraine Headache:<br>Some Clinical Observations on the<br>Vascular Mechanism and Its Control  | 990  | CLINTON, E., M. C. HULSE, N. WEISS-<br>MAN, E. STOTZ, — and J. W. FERRE-<br>BEE. Subclinical Vitamin Deficiency.<br>V. The Assay of Subclinical Thiamin<br>Deficiency.....  | 440 |
| BARNETT, R., S. L. ZIMMERMAN and —.<br>Sickle Cell Anemia Simulating Coro-<br>nary Occlusion. <i>Case Rep.</i> .....  | 1045 | COHN, T. D., G. KAPLAN and —. Syn-<br>drome of Auriculoventricular Acces-<br>sory Pathway.....  | 824 |
| BARR, D., F. FERGUSON and —. Gly-<br>cosuria in Meningitis.....   | 173  | CORCORAN, A. C. and I. H. PAGE. Dif-<br>ferential Diagnosis of Terminal Glo-<br>merulonephritis and Malignant Hy-<br>pertension. I. Renal Aspects.....  | 747 |
| BARRETT, T. F., J. S. SWEENEY, F. B.<br>QUEEN and —. Trichinosis: A Spo-<br>radic Outbreak with Report of a Case.<br><i>Case Rep.</i> .....   | 1037 | COSGRIFF, S. W. The Waterhouse-<br>Friderichsen Syndrome: Observations<br>on Associated Adrenal Insufficiency<br>and Report of Four Cases.....  | 187 |
| BELL, E. T. A Textbook of Pathology.<br><i>Rev.</i> .....   | 347  | COVE, A. M., E. H. GRIECO and —. Men-<br>ingococcic Meningitis—Sulfadiazine<br>Therapy (Review of Twenty Cases)..   | 194 |
| BETTMAN, R. B. and W. TANNENBAUM.<br>Ligation of Patent Ductus Arteriosus<br>in the Presence of an Apparent Bac-<br>terial Endocarditis: Report of a Case<br>Apparently Cured. <i>Case Rep.</i> ..... | 1035 | CRESS, C. H., F. B. CLARE, — and E.<br>GELLHORN. Leukocytosis and the<br>Sympathetico-Adrenal System.....   | 653 |
| BIERMAN, W. Physical Medicine in<br>General Practice. <i>Rev.</i> .....   | 725  |   |     |
| BINKLEY, B., W. R. ARROWSMITH, —<br>and C. V. MOORE. Fatal Agranulo-<br>cytosis Following the Intraperitoneal<br>Implantation of Sulfanilamide Crys-<br>tals. <i>Case Rep.</i> .....                  | 323  |   |     |
| BLUMBERG, H., A. H. RUSSAKOFF and<br>—. Choline as an Adjuvant to the   |      |   |     |



- DARLEY, W., R. W. GORDON and K. T. NEUBUERGER. Simmonds' Disease with Therapeutic Response to Hormone Therapy for Four Years: Report of a Case with Necropsy Findings. *Case Rep.*..... 890
- DEICHMANN, W. B., K. V. KITZMILLER, S. WITHERUP and R. JOHANSMANN. Kerosene Intoxication..... 803
- DERBES, V. J., H. T. ENGELHARDT and —. Spontaneous Pneumothorax and Bronchial Asthma. *Case Rep.*..... 711
- DONALD, D. and R. E. WUNSCH. Acute Hemolytic Anemia with Toxic Hepatitis Caused by Sulfadiazine. *Case Rep.*..... 709
- EICHERT, H. Wolff-Parkinson-White Syndrome Simulating Myocardial Infarction. *Case Rep.*..... 907
- ELWOOD, B. J. and I. E. GERBER. Large Interauricular Septal Defect Associated with Tuberculosis and Amyloidosis. *Case Rep.*..... 485
- ENGELHARDT, H. T. and V. J. DERBES. Spontaneous Pneumothorax and Bronchial Asthma. *Case Rep.*..... 711
- ERF, L. A., and P. A. HERBUT. Primary and Secondary Myelofibrosis (A Clinical and Pathological Study of Thirteen Cases of Fibrosis of the Bone Marrow)..... 863
- EVANS, C. L., Ed. Starling's Principles of Human Physiology. *Rev.*..... 497
- EVANS, W. E., JR., J. G. MCALPINE, B. SKITARELIC and E. H. TONOLLA. I. Treatment of Experimentally Produced Staphylococcal Thoracic Empyema..... 70
- EVERETT, H. S. Gynecological and Obstetrical Urology. *Rev.*..... 1054
- FAGIN, I. D. and F. M. THOMPSON. Cirrhosis of the Liver; An Analysis of 71 Cases..... 285
- FAUST, D. B., H. R. GILMORE, JR. and C. S. MUDGETT. Chordomata: A Review of the Literature with Report of a Sacrococcygeal Case. *Case Rep.*... 678
- FERGUSON, F. and D. BARR. Glycosuria in Meningitis..... 173
- FERREBEE, J. W., M. C. HULSE, N. WEISSMAN, E. STOTZ, M. CLINTON and —. Subclinical Vitamin Deficiency. V. The Assay of Subclinical Thiamin Deficiency..... 440
- FLEXNER, J., N. E. ROSSETT and —. The Effect of Certain Antacids in Man Measured by a Simplified Method for the Continuous Recording of Gastric pH..... 119
- FRIEDMAN, S. and P. D. WHITE. Rupture of the Heart in Myocardial Infarction. Experience in a Large General Hospital..... 778
- FROSCH, H. L. and W. HOROWITZ. Rupture of Abdominal Aorta into Duodenum (Through a Sinus Tract Created by a Tuberculous Mesenteric Lymphadenitis). *Case Rep.*..... 481
- GELLHORN, E., F. B. CLARE, C. H. CRESS and —. Leukocytosis and the Sympathetico-Adrenal System..... 653
- GERBER, I. E., B. J. ELWOOD and —. Large Interauricular Septal Defect Associated with Tuberculosis and Amyloidosis. *Case Rep.*..... 485
- GILMORE, H. R., JR., D. B. FAUST, — and C. S. MUDGETT. Chordomata: A Review of the Literature with Report of a Sacrococcygeal Case. *Case Rep.*..... 678
- GOLDMAN, A. and H. ROTH. Spontaneous Pneumothorax: A Report of Three Unusual Cases..... 1011
- GORDON, R. W., W. DARLEY, — and K. T. NEUBUERGER. Simmonds' Disease with Therapeutic Response to Hormone Therapy for Four Years: Report of a Case with Necropsy Findings. *Case Rep.*..... 890
- GRIECO, E. H. and A. M. COVE. Meningococcal Meningitis—Sulfadiazine Therapy (Review of Twenty Cases) 194
- HECHT, H. H., F. F. YONKMAN, P. H. NOTH and —. Demerol: A New Synthetic Analgetic, Spasmolytic and Sedative Agent. I. Pharmacologic Studies..... 7
- II. Clinical Observations..... 17
- HERBUT, P. A., L. A. ERF and —. Primary and Secondary Myelofibrosis (A Clinical and Pathological Study of Thirteen Cases of Fibrosis of the Bone Marrow)..... 863

- HERRMANN, G. R. Synopsis of Diseases of the Heart and Arteries. *Rev.*.... 917
- HINDLE, J. A., G. W. THORN, — and J. A. SANDMEYER. Pheochromocytoma of the Adrenal Associated with Persistent Hypertension. *Case Rep.* 122
- HOLMQUEST, H. J., S. L. OSBORNE and —. Technic of Electrotherapy and Its Physical and Physiological Basis. *Rev.*..... 722
- HOROWITZ, W., H. L. FROSCHE and —. Rupture of Abdominal Aorta into Duodenum (Through a Sinus Tract Created by a Tuberculous Mesenteric Lymphadenitis). *Case Rep.*..... 481
- HULSE, M. C., N. WEISSMAN, E. STOTZ, M. CLINTON and J. W. FERREBEE. Subclinical Vitamin Deficiency. V. The Assay of Subclinical Thiamin Deficiency..... 440
- JACOBSON, E. Direct Measurements of the Effects of Bromides, Sodium Amytal and of Caffeine in Man..... 455
- JAHSMAN, W. E. Chylothorax; Brief Review of Literature; Report of Three Non-Traumatic Cases. *Case Rep.*... 669
- JETTER, W. W. and P. D. WHITE. Rupture of the Heart in Patients in Mental Institutions..... 783
- JOHANSMANN, R., W. B. DEICHMANN, K. V. KITZMILLER, S. WITHERUP and —. Kerosene Intoxication..... 803
- JOHNSON, W., B. E. MALSTROM and B. W. VOLK. A Clinico-Pathologic Study of 100 Cases of Acute and Chronic Gall-Bladder Disease..... 431
- KAPLAN, G. and T. D. COHN. Syndrome of Auriculoventricular Accessory Pathway..... 824
- KASICH, M., S. SOLOMON, — and N. KIVEN. Periarteritis Nodosa, with Report of Three Cases Diagnosed during Life..... 638
- KATZENELBOGEN, S. Psychotherapy.. 412
- KAUFMAN, R. E. Heterophile Antibody Reaction in Infectious Mononucleosis 230
- KING, J. T., C. BRANWELL and —. The Principles and Practice of Cardiology. *Rev.*..... 917
- KIRBY, W. M. M. and C. D. ARMSTRONG. Sarcoidosis with Uveoparotid Fever. *Case Rep.*..... 475
- KITZMILLER, K. V., W. B. DEICHMANN, — S. WITHERUP and R. JOHANSMANN. Kerosene Intoxication..... 803
- KIVEN, N., S. SOLOMON, M. KASICH and —. Periarteritis Nodosa, with Report of Three Cases Diagnosed during Life..... 638
- KNIGHTON, J. E., O. A. PALATUCCI and —. Short P-R Interval Associated with Prolongation of QRS Complex: A Clinical Study Demonstrating Interesting Variations..... 58
- KOHLSTAEDT, K. G., R. D. TAYLOR, — A. B. RICHTER and I. H. PAGE. Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension. II. Cardiac Aspects.... 765
- KOVÁCS, R. A Manual of Physical Therapy. *Rev.*..... 724
- KRELL, S. Electrocardiographic Record of a Dying Heart. *Case Rep.*... 903
- KUGELMASS, I. N. Clinical Pediatrics. *Rev.*..... 153
- LEDERER, M., E. L. SHLEVIN and —. Uncontrollable Hemorrhage after Dicoumarol Therapy with Autopsy Findings. *Case Rep.*..... 332
- LEVINE, S. A. and W. B. LIKOFF. Some Notes on the Transmission of Heart Murmurs..... 298
- LIKOFF, W. B., S. A. LEVINE and —. Some Notes on the Transmission of Heart Murmurs..... 298
- MALSTROM, B. W., W. JOHNSON, — and B. W. VOLK. A Clinico-Pathologic Study of 100 Cases of Acute and Chronic Gall-Bladder Disease..... 431
- MAZER, M. and J. A. REISINGER. An Electrocardiographic Study of Cardiac Aging Based on Records at Rest and after Exercise..... 645
- MCALPINE, J. G., W. E. EVANS, JR., — B. SKITARELIC and E. H. TONOLLA. I. Treatment of Experimentally Produced Staphylococcal Thoracic Empyema..... 70
- MCCALL, M. and J. W. PENNOCK. Periarteritis Nodosa: Our Present Knowledge of the Disease..... 628
- MCINTIRE, R. T. The Great Need for Internists in the Naval Medical Program..... 1

- MEYER, O. O. and E. W. THEWLIS.  
The Leukocyte Count in Primary  
Atypical Pneumonia of Undetermined  
Etiology..... 977
- MILLER, H. Spontaneous Mediastinal  
Emphysema..... 998
- MOORE, C. V., W. R. ARROWSMITH, B.  
BINKLEY and —. Fatal Agranulocy-  
tosis Following the Intraperitoneal  
Implantation of Sulfanilamide Crys-  
tals. *Case Rep.*..... 323
- MOORE, N. S., H. B. SUTTON and —.  
The Diagnosis and Treatment of  
Congenital Hemolytic (Spherocytic)  
Jaundice: Report of a Case with Un-  
usual Blood Findings Altered by Liver  
Therapy. *Case Rep.*..... 698
- MOORMAN, L. J. Hemoptysis in Tuber-  
culosis, with a Differential Discussion  
of Other Causes..... 447
- MOREHEAD, R. P., F. R. TAYLOR and —.  
Spontaneous Complete Rupture of  
the Aorta without Dissecting Aneu-  
rysm, with Report of a Case Showing  
a New Physical Sign (Periaortic Fric-  
tion Rub)..... 81
- MUDGETT, C. S., D. B. FAUST, H. R.  
GILMORE, JR. and —. Chordomata:  
A Review of the Literature with Re-  
port of a Sacrococcygeal Case. *Case  
Rep.*..... 678
- MURPHY, F. D., E. J. O'DONOVAN and  
—. Extrarenal Uremia: Report of  
Two Cases Due to Pyloric Obstruc-  
tion..... 662
- NEUBUERGER, K. T., W. DARLEY, R.  
W. GORDON and —. Simmonds'  
Disease with Therapeutic Response  
to Hormone Therapy for Four Years:  
Report of a Case with Necropsy Find-  
ings. *Case Rep.*..... 890
- NOTH, P. H., F. F. YONKMAN, — and  
H. H. HECHT. Demerol: A New Syn-  
thetic Analgetic, Spasmolytic and  
Sedative Agent. I. Pharmacologic  
Studies..... 7  
II. Clinical Observations..... 17
- NOVAK, E. Textbook of Gynecology.  
*Rev.*..... 1053
- O'DONOVAN, E. J. and F. D. MURPHY:  
Extrarenal Uremia: Report of Two  
Cases Due to Pyloric Obstruction... 662
- OSBORNE, S. L. and H. J. HOLMQUEST.  
Technic of Electrotherapy and Its  
Physical and Physiological Basis.  
*Rev.*..... 722
- PAGE, I. H., A. C. CORCORAN and —.  
Differential Diagnosis of Terminal  
Glomerulonephritis and Malignant  
Hypertension. I. Renal Aspects.... 747
- PAGE, I. H., R. D. TAYLOR, K. G.  
KOHLESTAEDT, A. B. RICHTER and —.  
Differential Diagnosis of Terminal  
Glomerulonephritis and Malignant  
Hypertension. II. Cardiac Aspects: 765
- PALATUCCI, O. A. and J. E. KNIGHTON.  
Short P-R Interval Associated with  
Prolongation of QRS Complex: A  
Clinical Study Demonstrating Inter-  
esting Variations..... 58
- PEARSON, J. R. and A. W. WALLACE.  
The Syndrome of Paroxysmal Tachy-  
cardia with Short P-R Interval and  
Prolonged QRS Complex, with Re-  
port of Two Cases..... 830
- PEETE, D. C. Rheumatic Fever: Diet  
as a Predisposing Factor..... 44
- PENNOCK, J. W., M. MCCALL and —.  
Periarthritis Nodosa: Our Present  
Knowledge of the Disease..... 628
- PERKIN, F. S. Syphilis and Diabetes  
Mellitus; A Long-Term Clinical Study 272
- PILLSBURY, D. M., E. ROSE and —.  
Lupus Erythematosus (Erythema-  
todes) and Ovarian Function: Obser-  
vations on a Possible Relationship,  
with Report of Six Cases..... 1022
- POTTER, H. W. and L. H. BRONSTEIN.  
Some Clinical Characteristics of  
Mumps, and the Effect of Belladonna  
in Treatment: A Study Made at the  
Station Hospital, Fort George G.  
Meade, Maryland..... 469
- POTTER, H. W., R. D. REID and L. H.  
BRONSTEIN. Meningococcemia with-  
out Meningitis; A Study Made at the  
Station Hospital, Fort George G.  
Meade, Maryland..... 200
- POTTER, J. K. and R. J. WHITACRE.  
Dermatitis Due to Barbiturates: Re-  
port of a Case with Associated Ane-  
mia. *Case Rep.*..... 1041
- PROPP, S. and J. L. SCHWIND. Sternal  
Puncture as a Practical Diagnostic  
Procedure..... 580

- QUEEN, F. B., J. S. SWEENEY, — and T. F. BARRETT. Trichinosis: A Sporadic Outbreak with Report of a Case. *Case Rep.*..... 1037
- REID, R. D., H. W. POTTER, — and L. H. BRONSTEIN. Meningococccemia without Meningitis; A Study Made at the Station Hospital, Fort George G. Meade, Maryland..... 200
- REISINGER, J. A., M. MAZER and —. An Electrocardiographic Study of Cardiac Aging Based on Records at Rest and after Exercise..... 645
- RICHTER, A. B., R. D. TAYLOR, K. G. KOHLSTAEDT, — and I. H. PAGE. Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension. II. Cardiac Aspects. 765
- ROBBINS, S. L., C. B. CHAPMAN and —. Patent Ductus Arteriosus with Pulmonary Vascular Sclerosis and Cyanosis. *Case Rep.*..... 312
- ROSE, E. and D. M. PILLSBURY. Lupus Erythematosus (Erythematodes) and Ovarian Function: Observations on a Possible Relationship, with Report of Six Cases..... 1022
- ROSSETT, N. E. and J. FLEXNER. The Effect of Certain Antacids in Man Measured by a Simplified Method for the Continuous Recording of Gastric pH..... 119
- ROTH, H., A. GOLDMAN and —. Spontaneous Pneumothorax: A Report of Three Unusual Cases..... 1011
- RUSSAKOFF, A. H. and H. BLUMBERG. Choline as an Adjuvant to the Dietary Therapy of Cirrhosis of the Liver... 848
- SAMS, C. F. Medical Problems in the Middle East..... 215
- SANDMEYER, J. A., G. W. THORN, J. A. HINDLE and —. Pheochromocytoma of the Adrenal Associated with Persistent Hypertension. *Case Rep.*.... 122
- SCHEMM, F. R. A High Fluid Intake in the Management of Edema, Especially Cardiac Edema. II. Clinical Observations and Data..... 937
- SCHWEDEL, J. B., D. YOUNG and —. Longevity in Ventricular Aneurysm; Report of a Case Followed over a Ten Year Period. *Case Rep.*..... 141
- SCHWIND, J. L., S. PROPP and —. Sternal Puncture as a Practical Diagnostic Procedure..... 580
- SCOVEL, F. G. Kala Azar: A Review of Its Incidence and Epidemiology in China and Clinical Observations on 585 Cases..... 607
- SHLEVIN, E. L. and M. LEDERER. Uncontrollable Hemorrhage after Dicoumarol Therapy with Autopsy Findings. *Case Rep.*..... 332
- SKITARELIC, B., W. E. EVANS, JR., J. G. MCALPINE, — and E. H. TONOLLA. I. Treatment of Experimentally Produced Staphylococcal Thoracic Empyema..... 70
- SLOWEY, J. F. A Case of Transient Successive Pulmonary Infiltration (Loeffler's Syndrome) Associated with Trichiniasis. *Case Rep.*..... 130
- SMITH, H. W. and H. C. SOLOMON. Traumatic Neuroses in Court..... 367
- SMULL, K., C. P. VOLTZ and —. Hyperparathyroidism, with Failure to Recalcify after Removal of Parathyroid Adenoma. *Case Rep.*..... 329
- SOLOMON, H. C., H. W. SMITH and —. Traumatic Neuroses in Court..... 367
- SOLOMON, S., M. KASICH and N. KIVEN. Periarteritis Nodosa, with Report of Three Cases Diagnosed during Life.. 638
- STERN, F. Applied Dietetics. *Rev.*... 153
- STOTZ, E., M. C. HULSE, N. WEISSMAN, — M. CLINTON and J. W. FERREBEE. Subclinical Vitamin Deficiency. V. The Assay of Subclinical Thiamin Deficiency..... 440
- SUTTON, H. B. and N. S. MOORE. The Diagnosis and Treatment of Congenital Hemolytic (Spherocytic) Jaundice: Report of a Case with Unusual Blood Findings Altered by Liver Therapy. *Case Rep.*..... 698
- SWEENEY, J. S., F. B. QUEEN and T. F. BARRETT. Trichinosis: A Sporadic Outbreak with Report of a Case. *Case Rep.*..... 1037
- TANNENBAUM, W., R. B. BETTMAN and —. Ligation of Patent Ductus Arteriosus in the Presence of an Apparent Bacterial Endocarditis: Report of a Case Apparently Cured. *Case Rep.* 1035

- TAYLOR, F. R. and R. P. MOREHEAD. Spontaneous Complete Rupture of the Aorta without Dissecting Aneurysm, with Report of a Case Showing a New Physical Sign (Periaortic Friction Rub)..... 81
- TAYLOR, R. D., K. G. KOHLSTAEDT, A. B. RICHTER and I. H. PAGE. Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension. II. Cardiac Aspects. 765
- TEMPLETON, F. E. X-Ray Examination of the Stomach. *Rev.*..... 1053
- THEWLIS, E. W., O. O. MEYER and —. The Leukocyte Count in Primary Atypical Pneumonia of Undetermined Etiology..... 977
- THOMPSON, F. M., I. D. FAGIN and —. Cirrhosis of the Liver; An Analysis of 71 Cases..... 285
- THORN, G. W., J. A. HINDLE and J. A. SANDMEYER. Pheochromocytoma of the Adrenal Associated with Persistent Hypertension. *Case Rep.*..... 122
- TONOLLA, E. H., W. E. EVANS, JR., J. G. MCALPINE, B. SKITARELIC and —. I. Treatment of Experimentally Produced Staphylococcal Thoracic Empyema..... 70
- VOLK, B. W., W. JOHNSON, B. E. MALSTROM and —. A Clinico-Pathologic Study of 100 Cases of Acute and Chronic Gall-Bladder Disease..... 431
- VOLTZ, C. P. and K. SMULL. Hyperparathyroidism, with Failure to Recalcify after Removal of Parathyroid Adenoma. *Case Rep.*..... 329
- WAITZKIN, L. Impending Myocardial Infarction..... 421
- WALLACE, A. W., J. R. PEARSON and —. The Syndrome of Paroxysmal Tachycardia with Short P-R Interval and Prolonged QRS Complex, with Report of Two Cases..... 830
- WEINSTEIN, J. "Atypical" Coronary Disease in Young People..... 252
- WEISSMAN, N., M. C. HULSE, — E. STOTZ, M. CLINTON and J. W. FERREBEE. Subclinical Vitamin Deficiency. V. The Assay of Subclinical Thiamin Deficiency..... 440
- WHITACRE, R. J., J. K. POTTER and —. Dermatitis Due to Barbiturates: Report of a Case with Associated Anemia. *Case Rep.*..... 1041
- WHITE, P. D., S. FRIEDMAN and —. Rupture of the Heart in Myocardial Infarction. Experience in a Large General Hospital..... 778
- WHITE, P. D., W. W. JETTER and —. Rupture of the Heart in Patients in Mental Institutions..... 783
- WIRTSCHAFTER, Z. T. and R. WOLPAW. A Case of Nitrobenzene Poisoning. *Case Rep.*..... 135
- WITHERUP, S., W. B. DEICHMANN, K. V. KITZMILLER, — and R. JOHANSMANN. Kerosene Intoxication..... 803
- WOLPAW, R., Z. T. WIRTSCHAFTER and —. A Case of Nitrobenzene Poisoning. *Case Rep.*..... 135
- WOSIKA, P. H. An Evaluation of the Dark Test..... 101
- WUNSCH, R. E., D. DONALD and —. Acute Hemolytic Anemia with Toxic Hepatitis Caused by Sulfadiazine. *Case Rep.*..... 709
- YONKMAN, F. F., P. H. NOTH and H. H. HECHT. Demerol: A New Synthetic Analgetic, Spasmolytic and Sedative Agent. I. Pharmacologic Studies... 7  
II. Clinical Observations..... 17
- YOUNG, D. and J. B. SCHWEDEL. Longevity in Ventricular Aneurysm: Report of a Case Followed over a Ten Year Period. *Case Rep.*..... 141
- ZIMMERMAN, S. L. and R. BARNETT. Sick Cell Anemia Simulating Coronary Occlusion. *Case Rep.*..... 1045

# ANNALS OF INTERNAL MEDICINE

## SUBJECT INDEX

Volume 21, July-December, 1944

- A**BDOMINAL Aorta, Rupture of — into Duodenum (Through a Sinus Tract Created by a Tuberculous Mesenteric Lymphadenitis). H. L. FROSCH and W. HOROWITZ. *Case Rep.* 481
- Adrenal, Pheochromocytoma of the — Associated with Persistent Hypertension. G. W. THORN, J. A. HINDLE and J. A. SANDMEYER. *Case Rep.* 122
- Agranulocytosis, Fatal — Following the Intraperitoneal Implantation of Sulfanilamide Crystals. W. R. ARROWSMITH, B. BINKLEY and C. V. MOORE. *Case Rep.* 323
- Amylase, Serum — in Mumps. I. L. APFLEBAUM. 35
- Amyloidosis, Large Interauricular Septal Defect Associated with Tuberculosis and —. B. J. ELWOOD and I. E. GERBER. *Case Rep.* 485
- Anemia, Acute Hemolytic — with Toxic Hepatitis Caused by Sulfadiazine. D. DONALD and R. E. WUNSCH. *Case Rep.* 709
- Anemia, Report of a Case with Associated —. Dermatitis Due to Barbiturates: —. J. K. POTTER and R. J. WHITACRE. *Case Rep.* 1041
- Anemia, Sickle Cell — Simulating Coronary Occlusion. S. L. ZIMMERMAN and R. BARNETT. *Case Rep.* 1045
- Aneurysm, Longevity in Ventricular —: Report of a Case Followed over a Ten Year Period. D. YOUNG and J. B. SCHWEDEL. *Case Rep.* 141
- Antacids in Man, The Effect of Certain — as Measured by a Simplified Method for the Continuous Recording of Gastric pH. N. E. ROSSETT and J. FLEXNER. 119
- Aorta, Spontaneous Complete Rupture of the — without Dissecting Aneurysm with Report of a Case Showing a New Physical Sign (Periaortic Friction Rub). F. R. TAYLOR and R. P. MOREHEAD. 81
- Arteries, Synopsis of Diseases of the Heart and —. G. R. HERRMANN. *Rev.* 917
- Asthma, Spontaneous Pneumothorax and Bronchial —. H. T. ENGELHARDT and V. J. DERBES. *Case Rep.* 711
- Auriculoventricular Accessory Pathway, Syndrome of —. G. KAPLAN and T. D. COHN. 824
- B**ACTERIAL Endocarditis, Ligation of Patent Ductus Arteriosus in the Presence of an Apparent —: Report of a Case Apparently Cured. R. B. BETTMAN and W. TANNENBAUM. *Case Rep.* 1035
- Barbiturates, Dermatitis Due to —: Report of a Case with Associated Anemia. J. K. POTTER and R. J. WHITACRE. *Case Rep.* 1041
- Belladonna, Some Clinical Characteristics of Mumps, and the Effect of — in Treatment; A Study Made at the Station Hospital, Fort George G. Meade, Maryland. H. W. POTTER and L. H. BRONSTEIN. 469
- Benzedrine Sulfate in Obesity, The Use of —. F. K. ALBRECHT. 983
- Bromides, Direct Measurements of the Effects of —, Sodium Amytal and of Caffeine in Man. E. JACOBSON. 455
- Bronchiectasis, Roles of Medicine and Surgery in the Management of —. J. ALEXANDER. 565
- C**AFFEINE, Direct Measurements of the Effects of Bromides, Sodium Amytal and of — in Man. E. JACOBSON. 455
- Cardiac Aging, An Electrocardiographic Study of — Based on Records at Rest and after Exercise. M. MAZER and J. A. REISINGER. 645
- Cardiology, The Principles and Practice of —. C. BRAMWELL and J. T. KING. *Rev.* 917

- Cerebral Vascular Lesions in Rheumatic Fever. *Edit.*..... 494
- Choline as an Adjuvant to the Dietary Therapy of Cirrhosis of the Liver. A. H. RUSSAKOFF and H. BLUMBERG 848
- Chordomata: A Review of the Literature, with Report of a Sacrococcygeal Case. D. B. FAUST, H. R. GILMORE, JR. and C. S. MUDGETT. *Case Rep.*... 678
- Chylothorax: Brief Review of Literature; Report of Three Non-Traumatic Cases. W. E. JAHSMAN. *Case Rep.* 669
- Cirrhosis of the Liver; An Analysis of 71 Cases. I. D. FAGIN and F. M. THOMPSON..... 285
- Clinical Pediatrics. I. N. KUGELMASS. *Rev.*..... 153
- Coronary Disease, "Atypical" — in Young People., J. WEINSTEIN..... 252
- Coronary Occlusion, Sickle Cell Anemia Simulating —. S. L. ZIMMERMAN and R. BARNETT. *Case Rep.*..... 1045
- Cushing's Syndrome. *Edit.*..... 1050
- D**ARK Test, An Evaluation of the —. P. H. WOSIKA..... 101
- Demerol: A New Synthetic Analgetic, Spasmolytic and Sedative Agent. I. Pharmacologic Studies. F. F. YONKMAN, P. H. NOTH and H. H. HECHT. 7. II. Clinical Observations. P. H. NOTH, H. H. HECHT and F. F. YONKMAN..... 17
- Dermatitis Due to Barbiturates: Report of a Case with Associated Anemia. J. K. POTTER and R. J. WHITACRE. *Case Rep.*..... 1041
- Diabetes Mellitus, Syphilis and —: A Long-Term Clinical Study. F. S. PERKIN..... 272
- Dicoumarol Therapy, Uncontrollable Hemorrhage after — with Autopsy Findings. E. L. SHLEVIN and M. LEDERER. *Case Rep.*..... 332
- Dietary Factor in the Etiology of Pernicious Anemia, The —. J. M. ASKEY..... 402
- Dietetics, Applied —. F. STERN. *Rev.* 153
- Ductus Arteriosus, Ligation of Patent — in the Presence of an Apparent Bacterial Endocarditis: Report of a Case Apparently Cured. R. B. BETTMAN and W. TANNENBAUM. *Case Rep.*..... 1035
- Ductus Arteriosus, Patent — with Pulmonary Vascular Sclerosis and Cyanosis. C. B. CHAPMAN and S. L. ROBBINS. *Case Rep.*..... 312
- E**DEMA, A High Fluid Intake in the Management of —, Especially Cardiac Edema. II. Clinical Observations and Data. F. R. SCHEMM..... 937
- Electrocardiographic Record of a Dying Heart. S. KRELL. *Case Rep.*..... 903
- Electrocardiographic Study of Cardiac Aging Based on Records at Rest and after Exercise, An —. M. MAZER and J. A. REISINGER..... 645
- Electrotherapy, Technic of — and Its Physical and Physiological Basis. S. L. OSBORNE and H. J. HOLMQUEST. *Rev.*..... 722
- Emphysema, Spontaneous Mediastinal —. H. MILLER..... 998
- Empyema, The Treatment of Experimentally Produced Staphylococcal Thoracic —. I. W. E. EVANS, JR., J. G. McALPINE, B. SKITARELIC and E. H. TONOLLA..... 70
- G**ALL-BLADDER Disease, A Clinico-Pathologic Study of 100 Cases of Acute and Chronic —. W. JOHNSON, B. E. MALSTROM and B. W. VOLK..... 431
- Gastric pH, The Effect of Certain Antacids in Man as Measured by a Simplified Method for the Continuous Recording of —. N. E. ROSSETT and J. FLEXNER..... 119
- Glomerulonephritis, Differential Diagnosis of Terminal — and Malignant Hypertension. I. Renal Aspects. A. C. CORCORAN and I. H. PAGE..... 747
- II. Cardiac Aspects. R. D. TAYLOR, K. G. KOHLSTAEDT, A. B. RICHTER and I. H. PAGE..... 765
- Glycosuria in Meningitis. F. FERGUSON and D. BARR..... 173
- Gynecological and Obstetrical Urology. H. S. EVERETT. *Rev.*..... 1054
- Gynecology, Textbook of —. E. NOVAK. *Rev.*..... 1053
- H**EART and Arteries, Synopsis of Diseases of the —. G. R. HERRMANN. *Rev.*..... 917

- Heart Murmurs, Some Notes on the Transmission of —. S. A. LEVINE and W. B. LIKOFF..... 298
- Heart, Rupture of the — in Myocardial Infarction. Experience in a Large General Hospital. S. FRIEDMAN and P. D. WHITE..... 778
- Heart, Rupture of the — in Patients in Mental Institutions. W. W. JETTER and P. D. WHITE..... 783
- Hemoptysis in Tuberculosis, with a Differential Discussion of Other Causes. L. J. MOORMAN..... 447
- Hemorrhage, Uncontrollable — after Dicoumarol Therapy with Autopsy Findings. E. L. SHLEVIN and M. LEDERER. *Case Rep.*..... 332
- Hepatitis, Acute Hemolytic Anemia with Toxic — Caused by Sulfadiazine. D. DONALD and R. E. WUNSCH. *Case Rep.*..... 709
- Heterophile Antibody Reaction in Infectious Mononucleosis. R. E. KAUFMAN 230
- Histoplasmosis. *Edit.*..... 343
- Hormone Therapy, Simmonds' Disease with Therapeutic Response to — for Four Years: Report of a Case with Necropsy Findings. W. DARLEY, R. W. GORDON and K. T. NEUBUERGER. *Case Rep.*..... 890
- Hyperparathyroidism, with Failure to Recalcify after Removal of Parathyroid Adenoma. C. P. VOLTZ and K. SMULL. *Case Rep.*..... 329
- Hypertension, Differential Diagnosis of Terminal Glomerulonephritis and Malignant —: I. Renal Aspects. A. C. CORCORAN and I. H. PAGE..... 747
- II. Cardiac Aspects. R. D. TAYLOR, K. G. KOHLSTAEDT, A. B. RICHTER and I. H. PAGE..... 765
- Hypertension, Pheochromocytoma of the Adrenal Associated with Persistent —. G. W. THORN, J. A. HINDLE and J. A. SANDMEYER. *Case Rep.*... 122
- I**NTERAURICULAR Septal Defect, Large — Associated with Tuberculosis and Amyloidosis. B. J. ELWOOD and I. E. GERBER. *Case Rep.*..... 485
- J**AUNDICE, The Diagnosis and Treatment of Congenital Hemolytic (Spherocytic) —; Report of a Case with Unusual Blood Findings Altered by Liver Therapy. H. B. SUTTON and N. S. MOORE. *Case Rep.*..... 698
- K**ALA Azar: A Review of Its Incidence and Epidemiology in China and Clinical Observations on 585 Cases. F. G. SCOVEL..... 607
- Kerosene Intoxication. W. B. DEICHMANN, K. V. KITZMILLER, S. WITHERUP and R. JOHNSMANN..... 803
- L**EUKOCYTE Count in Primary Atypical Pneumonia of Undetermined Etiology, The —. O. O. MEYER and E. W. THEWLIS..... 977
- Leukocytosis and the Sympathetic-Adrenal System. F. B. CLARE, C. H. CRESS and E. GELLHORN..... 653
- Liver, Choline as an Adjuvant to the Dietary Therapy of Cirrhosis of the —. A. H. RUSSAKOFF and H. BLUMBERG..... 848
- Liver, Cirrhosis of the —; An Analysis of 71 Cases. I. D. FAGIN and F. M. THOMPSON..... 285
- Longevity in Ventricular Aneurysm; Report of a Case Followed over a Ten Year Period. D. YOUNG and J. B. SCHWEDEL. *Case Rep.*..... 141
- Lupus Erythematosus (Erythematoses) and Ovarian Function: Observations on a Possible Relationship, with Report of Six Cases. E. ROSE and D. M. PILLSBURY..... 1022
- M**EDICAL Problems in the Middle East. C. F. SAMS..... 215
- Meningitis, Glycosuria in —. F. FERGUSON and D. BARR..... 173
- Meningococcemia without Meningitis: A Study Made at the Station Hospital, Fort George Meade, Maryland. H. W. POTTER, R. D. REID and L. H. BRONSTEIN..... 200
- Meningococcic Meningitis — Sulfadiazine Therapy (Review of Twenty Cases). E. H. GRIECO and A. M. COVE 194
- Migraine Headache: Some Clinical Observations on the Vascular Mechanism and Its Control. M. ATKINSON 990
- Mononucleosis, Heterophile Antibody Reaction in Infectious —. R. E. KAUFMAN..... 230



- Mumps, Serum Amylase in —. I. L. APPLEBAUM..... 35
- Mumps, Some Clinical Characteristics of —, and the Effect of Belladonna in Treatment; A Study Made at the Station Hospital, Fort George G. Meade, Maryland. H. W. POTTER and L. H. BRONSTEIN..... 469
- Myelofibrosis, Primary and Secondary — (A Clinical and Pathological Study of Thirteen Cases of Fibrosis of the Bone Marrow). L. A. ERF and P. A. HERBUT..... 863
- Myocardial Infarction, Impending —. L. WAITZKIN..... 421
- Myocardial Infarction, Rupture of the Heart in —. Experience in a Large General Hospital. S. FRIEDMAN and P. D. WHITE..... 778
- Myocardial Infarction, Wolff-Parkinson-White Syndrome Simulating —. H. EICHERT. *Case Rep.*..... 907
- N**AVAL Medical Program, The Great Need for Internists in the —. R. T. MCINTIRE..... 1
- Neuroses, Traumatic — in Court. H. W. SMITH and H. C. SOLOMON..... 367
- Nitrobenzene Poisoning, A Case of —. Z. T. WIRTSCHAFTER and R. WOLPAW. *Case Rep.*..... 135
- Nutrition, Handbook of —. *Rev.*..... 347
- O**BESITY, The Use of Benzedrine Sulfate in —. F. K. ALBRECHT.. 983
- Obituaries:
- Albl, Michael Albert..... 168
- Bell, Harry J..... 172
- Biddle, Andrew Porter..... 931
- Breed, William B..... 742
- Butler, Rear Admiral Charles St. John 1078
- Cocke, Charles Hartwell..... 519
- Crawford, Hugh Francis..... 168
- Cunningham, Robert L..... 935
- Dennis, Foster Leonard..... 933
- Dunham, Kennon..... 517
- Gager, Edward C..... 1077
- Green, Edward Melvin..... 1080
- Gutman, Jacob..... 171
- Homan, Charles Edwin, Jr..... 745
- Hubbard, William Stimpson..... 744
- Hutchison, George McClintock..... 517
- Klemmer, Roland N..... 169
- Leroy, Louis..... 746
- MacKay, Angus..... 517
- MacNevin, Malcolm Graeme..... 936
- Madigan, Patrick S..... 365
- McMullen, Clarence James..... 366
- McNamara, Francis Patrick..... 936
- McSweeney, Edward Shearman..... 1076
- Meengs, Jacob Earl..... 170
- Milne, Lindsay Stephen..... 1075
- Murphy, John Thomas..... 930
- Nesbit, William Edward..... 168
- Richter, Harry Allen..... 1076
- Scott, James W..... 745
- Sherrick, Joseph Leslie..... 933
- Silverman, Isaac Judah..... 743
- Simpson, Virgil Earl..... 167
- Smith, Arthur Montell..... 1075
- Traynor, Joseph P..... 932
- Wakeman, Frank Bolles..... 170
- Walsh, Groesbeck Francis..... 931
- Watson, Lester Dow..... 744
- Wilson, Franklin Davis..... 934
- Woolery, Homer..... 518
- Obstetrical Urology, Gynecological and —. H. S. EVERETT. *Rev.*..... 1054
- Ovarian Function, Lupus Erythematosus (Erythematoses) and —: Observations on a Possible Relationship, with Report of Six Cases. E. ROSE and D. M. PILLSBURY..... 1022
- P**ARATHYROID Adenoma, Hyperparathyroidism with Failure to Calcify after Removal of —. C. P. VOLTZ and K. SMULL. *Case Rep.*..... 329
- Pathology, A Textbook of —. E. T. BELL. *Rev.*..... 347
- Pediatrics, Clinical —. I. N. KUGELMASS. *Rev.*..... 153
- Periarteritis Nodosa: Our Present Knowledge of the Disease. M. McCALL and J. W. PENNOCK..... 628
- Pernicious Anemia, The Dietary Factor in the Etiology of —. J. M. ASKEY.. 402
- Pheochromocytoma of the Adrenal Associated with Persistent Hypertension. G. W. THORN, J. A. HINDLE and J. A. SANDMEYER. *Case Rep.*... 122
- Physical Medicine in General Practice. W. BIERMAN. *Rev.*..... 725
- Physical Therapy, A Manual of —. R. KOVÁCS. *Rev.*..... 724
- Physiology, Starling's Principles of Human —. C. L. EVANS, Ed. *Rev.*... 497
- Pneumonia, The Leukocyte Count in Primary Atypical — of Undetermined

- Etiology. O. O. MEYER and E. W. THEWLIS..... 977
- Pneumothorax, Spontaneous — and Bronchial Asthma. H. T. ENGELHARDT and V. J. DERBES. *Case Rep.* 711
- Pneumothorax, Spontaneous —: A Report of Three Unusual Cases. A. GOLDMAN and H. ROTH..... 1011
- Poisoning, A Case of Nitrobenzene —. Z. T. WIRTSCHAFTER and R. WOLPAW. *Case Rep.*..... 135
- P-R Interval, Short — Associated with Prolongation of QRS Complex; A Clinical Study Demonstrating Interesting Variations. O. A. PALATUCCI and J. E. KNIGHTON..... 58
- Psychosomatic Medicine. *Edit.*..... 150
- Psychotherapy. S. KATZENELBOGEN.. 412
- Pulmonary Infiltration, A Case of Transient Successive — (Loeffler's Syndrome) Associated with Trichiniasis. J. F. SLOWEY. *Case Rep.*..... 130
- R**HEUMATIC Fever, Cerebral Vascular Lesions in —. *Edit.*..... 494
- Rheumatic Fever: Diet as a Predisposing Factor. D. C. PEETE..... 44
- Rheumatic Fever, Salicylates in the Treatment of —. *Edit.*..... 718
- Rupture of the Aorta, Spontaneous Complete — without Dissecting Aneurysm with Report of a Case Showing a New Physical Sign (Periaortic Friction Rub). F. R. TAYLOR and R. P. MOREHEAD..... 81
- Rupture of the Heart in Myocardial Infarction. Experience in a Large General Hospital. S. FRIEDMAN and P. D. WHITE..... 778
- Rupture of the Heart in Patients in Mental Institutions. W. W. JETTER and P. D. WHITE..... 783
- S**ALICYLATES in the Treatment of Rheumatic Fever. *Edit.*..... 718
- Sarcoidosis with Uveoparotid Fever. W. M. M. KIRBY and C. D. ARMSTRONG. *Case Rep.*..... 475
- Sclerosis, Patent Ductus Arteriosus with Pulmonary Vascular — and Cyanosis. C. B. CHAPMAN and S. L. ROBBINS. *Case Rep.*..... 312
- Serum Amylase in Mumps. I. L. APPLEBAUM..... 35
- Sickle Cell Anemia Simulating Coronary Occlusion. S. L. ZIMMERMAN and R. BARNETT. *Case Rep.*..... 1045
- Simmonds' Disease with Therapeutic Response to Hormone Therapy for Four Years: Report of a Case with Necropsy Findings. W. DARLEY, R. W. GORDON and K. T. NEUBUERGER. *Case Rep.*..... 890
- Sodium Amytal, Direct Measurements of the Effects of Bromides, — and of Caffeine in Man. E. JACOBSON..... 455
- Staphylococcal Thoracic Empyema, The Treatment of Experimentally Produced —. I. W. E. EVANS, JR., J. G. McALPINE, B. SKITARELIC and E. H. TONOLLA..... 70
- Starling's Principles of Human Physiology. C. L. EVANS, Ed. *Rev.*..... 497
- Sternal Puncture as a Practical Diagnostic Procedure. S. PROPP and J. L. SCHWIND..... 580
- Stomach, X-Ray Examination of the —. F. E. TEMPLETON. *Rev.*..... 1053
- Sulfadiazine, Acute Hemolytic Anemia with Toxic Hepatitis Caused by —. D. DONALD and R. E. WUNSCH. *Case Rep.*..... 709
- Sulfadiazine Therapy, Meningococcal Meningitis — (Review of Twenty Cases). E. H. GRIECO and A. M. COVE..... 194
- Sulfanilamide Crystals, Fatal Agranulocytosis Following the Intraperitoneal Implantation of —. W. R. ARROWSMITH, B. BINKLEY and C. V. MOORE. *Case Rep.*..... 323
- Sympathetico-Adrenal System, Leukocytosis and the —. F. B. CLARE, C. H. CRESS and E. GELLHORN..... 653
- Syndrome of Auriculoventricular Accessory Pathway. G. KAPLAN and T. D. COHN..... 824
- Syndrome of Paroxysmal Tachycardia with Short P-R Interval and Prolonged QRS Complex, with Report of Two Cases, The —. J. R. PEARSON and A. W. WALLACE..... 830
- Syphilis and Diabetes Mellitus: A Long-Term Clinical Study. F. S. PERKIN. 272
- T**ACHYCARDIA, The Syndrome of Paroxysmal — with Short P-R Interval and Prolonged QRS Com-

- plex, with Report of Two Cases. J. R. PEARSON and A. W. WALLACE... 830
- Thiamin Deficiency, The Assay of Subclinical —. Subclinical Vitamin Deficiency. V. —. M. C. HULSE, N. WEISSMAN, E. STOTZ, M. CLINTON and J. W. FERREBEE... 440
- Traumatic Neuroses in Court. H. W. SMITH and H. C. SOLOMON... 367
- Trichiniasis, A Case of Transient Successive Pulmonary Infiltration (Loeffler's Syndrome) Associated with —. J. F. SLOWEY. *Case Rep.*... 130
- Trichinosis: A Sporadic Outbreak with Report of a Case. J. S. SWEENEY, F. B. QUEEN and T. F. BARRETT. *Case Rep.*... 1037
- Tuberculosis and Amyloidosis, Large Interauricular Septal Defect Associated with —. B. J. ELWOOD and I. E. GERBER. *Case Rep.*... 485
- Tuberculosis, Hemoptysis in —, with a Differential Discussion of Other Causes. L. J. MOORMAN... 447
- Tuberculous Mesenteric Lymphadenitis, Rupture of Abdominal Aorta into Duodenum (Through a Sinus Tract Created by a —. H. L. FROSCH and W. HOROWITZ. *Case Rep.*... 481
- UREMIA, Extrarenal —: Report of Two Cases Due to Pyloric Obstruction. E. J. O'DONOVAN and F. D. MURPHY... 662
- Urology, Gynecological and Obstetrical —. H. S. EVERETT. *Rev.*... 1054
- Uveoparotid Fever, Sarcoidosis with —. W. M. M. KIRBY and C. D. ARMSTRONG. *Case Rep.*... 475
- VITAMIN Deficiency, Subclinical —. V. The Assay of Subclinical Thiamin Deficiency. M. C. HULSE, N. WEISSMAN, E. STOTZ, M. CLINTON and J. W. FERREBEE... 440
- Vitamins, Rational Use of the —. *Edit.* 913
- WATERHOUSE Friderichsen Syndrome, The —: Observations on Associated Adrenal Insufficiency and Report of Four Cases. S. W. COSGRIFF... 187
- Wolff-Parkinson-White Syndrome Simulating Myocardial Infarction. H. EICHERT. *Case Rep.*... 907
- X-RAY Examination of the Stomach. F. E. TEMPLETON. *Rev.*... 1053

